METTL14-mediated RNA methylation in digestive system tumors

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Abstract. N6-methyladenosine (m6A) RNA methylation is one of the most common post-transcriptional modification mechanism in eukaryotes. m6A is involved in almost all stages of the mRNA life cycle, specifically regulating its stability, splicing, export and translation. Methyltransferase-like 14 (METTL14) is a particularly important m6A methylation 'writer' that can recognize RNA substrates. METTL14 has been documented to improve the activity and catalytic efficiency of METTL3. However, as individual proteins they can also regulate different biological processes. Malignancies in the digestive system are some of the most common malignancies found in humans, which are typically associated with poor prognoses with limited clinical solutions. METTL14-mediated methylation has been implicated in both the potentiation and inhibition of digestive system tumor growth, cell invasion and metastasis, in addition to drug resistance. In the present review, the research progress and regulatory mechanisms of METTL14-mediated methylation in digestive system malignancies were summarized. In addition, future research directions and the potential for its clinical application were examined.

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1. Introduction

Epigenetics is the study of heritable phenotypes that do not involve changes in the actual nuclear DNA sequence (1-4). Examples of known epigenetic modulations include DNA methylation, expression interference by non-coding RNAs (ncRNA) and histone modifications (5-8). Genetic information is encoded by DNA, which is transcribed into coding mRNA or non-coding RNA. mRNA is then translated into functional proteins (9). Epigenetic inheritance not only serves a role in transcription and translation, but is also involved in post-transcriptional mRNA regulation (10).

Some of the most commonly studied RNA methylation modification processes include N6-methyladenosine (m6A), 5-methylcytosine (m5C) and 7-methylguanosine (m7G) (11). m6A is the most common epigenetic modification mechanism of RNA molecules, which was first identified in eukaryotic mRNAs in the early 1970s (12). In 2011, it was then discovered that the m6A process is reversible, when fat mass and obesity-associated (FTO) protein was shown to function as an m6A mRNA demethylase (13).

m6A methylation was subsequently found to occur in all species of eukaryotes, prokaryotes and viruses (14,15). m6A modifications can occur on mRNAs, ribosomal (rRNAs), small nuclear (snRNAs) and microRNAs (miRNAs) (16). To date, m6A sites have been identified in >7,000 coding RNAs and 300 non-coding RNAs (17,18). Functionally, m6A can regulate almost all processes during the mRNA life cycle, including stability, splicing, export and translation (19,20). m6A modifications generally occur on 'RRACH' RNA sequences, where R can be A or G bases and H can be A, C or U bases (21). Qualcomm test sequencing previously revealed that the m6A signals typically clustered near the 3'-untranslated region (UTR) and stop codons (22). This likely aids in maintaining the structural stability of the mRNA (22). By contrast, clustering near the 5'-UTR or long internal exons is considered to be involved in mRNA splicing, translation and degradation (23-25). Specifically, YTH domain-family proteins (YTHD) 2 can bind m6A in the 5'-UTR of mRNAs, promoting their cap-independent translation. mRNAs containing the m6A modification in the 5'-UTR can be identified to promote cap-independent translation initiation by direct binding to eukaryotic initiation factor (eIF)3 (23).

At present, m6A regulators can be classified into methyltransferases ('writers'), demethylases ('erasers') and RNA-binding proteins ('readers') (26). Specifically, 'Writers' catalyze m6A methylation and include

methyltransferase-like (METTL) proteins, such as METTL3 (27-29), METTL14 (30,31), METTL16 (32,33), Wilms tumor 1-associated protein (WTAP) (26,34,35), RNA-binding motif protein 15 (26) and Vir-like m6A methyltransferase (36-38). Alternatively, 'erasers', such as FTO, AlkB homolog (ALKBH)3 and ALKBH5, generally catalyze the demethylation of m6A residues in an iron (II) and α-ketoglutarate-dependent manner (39-42). The renders m6A methylation to be a dynamically reversible process (10). The role of 'readers' are to identify the methylation modifications and transmit regulatory signals to downstream functional proteins to facilitate various biological processes, such as RNA splicing, stabilization, export and mRNA translation (21,43). Such 'readers' include YTHDC1/2 and YTHDF1/2/3 (44,45), heterogenous nuclear ribonucleoproteins (hnRNP)C, hnRNPG and hnRNPA2B1 (46), eIF3 (38) and insulin-like growth factor-2 mRNA-binding proteins (IGF2BP; Fig. 1) (44,47).

2. METTL3/METTL14-mediated RNA methylation

The m6A methylation 'writer' METTL14 has been characterized to be a weak methyltransferase that cannot catalyze methylation independently (6). Complete catalysis is achieved by the METTL3/METTL14 complex, a stoichiometrically 1:1 heterodimer (48). These two methylase components were initially discovered by isolating nuclear extracts from HeLa cells, such that the key 70-kDa METTL3 subunit was extracted from the 200-kDa mRNA adenosine methylase complex (49). Through its open methyltransferase domain (MTD), the internal DPPW motif on METTL3 binds to the free methyl donor S-adenosylmethionine methionine (SAM) to generate the metabolite S-adenosine homocysteine (SAH). SAH then competitively regulates methylation homeostasis, by promoting the association of the tyrosine residue Y406 on the METTL3 with the mRNA (50,51). By contrast, METTL14 also contains an MTD, but its EPPL motif that confers catalytic cavity adopts a closed conformation, obstructing its access to SAM (52,53). Additionally, METTL3 has a unique Cys-Cys-Cys-His (CCCH)-type zinc-binding motif, which has been reported to bind nucleic acids and be required for RNA methyltransferase activity (50,54,55). The current working model of this METTL3/METTL14 complex is that the main function of METTL14 is to recognize the RNA substrate whilst enhancing the activity and catalytic efficiency of METTL3 (52). However, METTL3 and METTL14 have also been found to serve opposing regulatory roles in cancer. One previous study found the opposite expression and prognostic value of METTL3 and METTL14 in hepatocellular carcinoma (HCC) (56). In addition, separately downregulating the expression of METTL3 and METTL14 resulted in the alteration of distinct mRNA signaling pathways and biological processes in HCC (56). Apart from METTL3/METTL14 dimerization, WTAP can contribute to METTL3/METTL14 complex stabilization and localization to the nucleus (57,58).

3. METTL3/METTL14 and digestive system cancer

Lin *et al* (59) previously found that in gallbladder cancer, deoxycholic acid can bind to the METTL3/METTL14 complex, promoting METTL3 separation to enhance the expression of miR-92b-3p (59). Furthermore, another previous study on liver cancer found that thiamine treatment enhanced METTL3 acetylation, which weakened its binding to METTL14 to reduce the expression of metal regulatory transcription factor (*MTF1*) mRNA (60). However, it also extended the half-life of this mRNA transcript, which in turn promoted MTF1 protein expression (60). Overexpression of MTF1 was therefore proposed to be a marker of HCC proliferation and consequently poor prognosis.

4. Roles of METTL14 in digestive system cancer

During neoplastic transformation, m6A modification can regulate tumor development and progression by modulating the structures of oncogene and suppressor gene mRNAs (4,61-63). Recently, various studies have reported that METTL14 can serve a diverse array of roles in digestive system malignancies, including regulation of proliferation, invasion, metastasis, angiogenesis and drug resistance. Therefore, current research progress (until December 2022) on the functions of METTL14 in digestive system tumors was summarized in this section and Table I.

Gastric cancer. To date, great progress has been made in the development of treatment methods for gastric cancer (GC). Immuno- and targeted therapies have contributed favorably to the prognosis of patients with GC. However, the mortality rate from GC remains to rank highly in China, ranking second after lung cancer in 2022. This is due in part to its high propensity for metastasis and invasion (64,65). m6A RNA methylation has been previously associated with the occurrence and aggressiveness of GC (66).

Zhang *et al* (67) found that knocking down *METTL14* expression can activate Wnt and PI3K/Akt signaling, which in turn promoted GC cell proliferation and invasion (67). METTL14 downregulation also resulted in the increased levels of secreted IFN-α/β/γ proteins in the HGC27 cell line. As such, it was speculated that RNA m6A methylation can regulate the immune response to GC by inhibiting IFN production. In addition, another study previously reported that in GC tissues, METTL14 expression and m6A levels were lower compared with those in adjacent tissues (68). By contrast, METTL14 overexpression was found to inhibit GC cell proliferation and invasion *in vitro* (68). Mechanistically, METTL14 downregulation increased the phosphorylation levels of PI3K, AKT and mTOR, whilst increasing the expression of vimentin, N-cadherin and MMP9, but decreased the expression of E-cadherin (68). Taken together, these findings suggest that METTL14 overexpression may inhibit the progression and aggressiveness of GC cells by inactivating the PI3K/AKT/mTOR and epithelial-mesenchymal transition (EMT) pathways. Yao *et al* (69) previously demonstrated that significantly lower METTL14 expression levels in stomach adenocarcinoma (STAD) tissues are associated with poorer prognosis (69). Overexpression of METTL14 was observed to enhance the stability of *PTEN* mRNA in a m6A modification-dependent manner, which prolonged its half-life (69). Further *in vivo* and *in vitro* experiments revealed that this METTL14-enhanced *PTEN* expression also inhibited the proliferative and invasive capabilities of STAD cells (69).

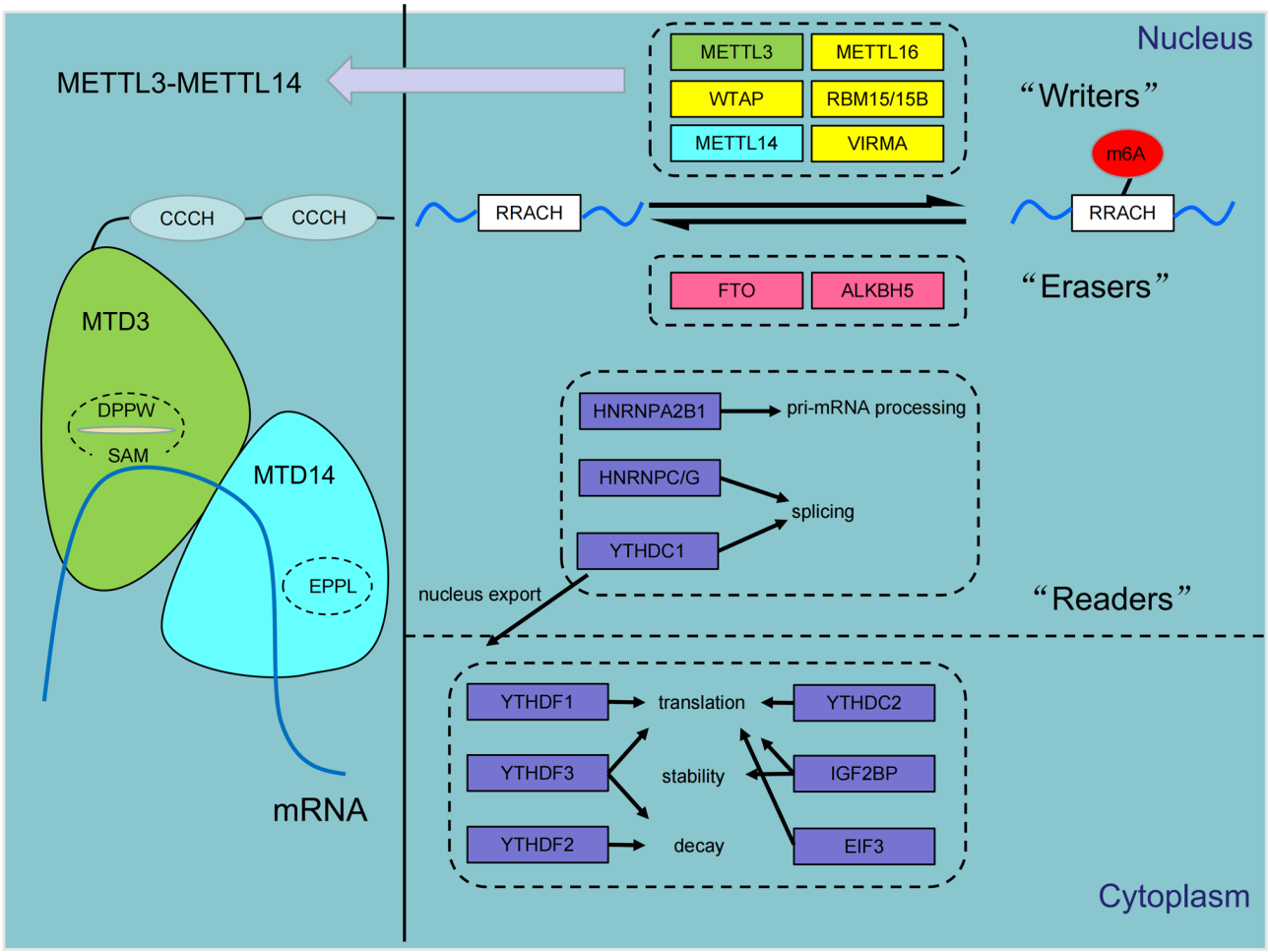

Figure 1. Schematic of the modification mechanism of m6A methylation. 'Writers' (yellow, green or aqua rectangles) catalyze methylation by adding the methyl group (red oval) to the adenine base. 'Erasers' (pink rectangles) remove the methyl group (red oval) from the methylation sites. 'Readers' (purple rectangles) recognize these signals and regulate downstream protein functions. The METTL3/METTL14 'writer' complex recognizes RNA substrate and exerts a catalytic effect. METTL, methyltransferase-like; MTD3, methyltransferase domain; SAM, S-adenosylmethionine methionine; WTAP, Wilms tumor 1-associated protein; RBM, RNA-binding motif protein; VIRMA, Vir-Like m6A methyltransferase-associated; FTO, fat mass and obesity-associated; ALKBH5, AlkB homolog 5; HNRNP, heterogenous nuclear ribonucleoproteins; YTHD, YTH domain-containing/family proteins; IGF2BP, insulin-like growth factor-2 mRNA-binding proteins; EIF3, eukaryotic initiation factor 3.

IGF2BP2 and IGF2BP3 were also shown to be 'readers' that can interact with the *PTEN* mRNA (69). Fan *et al* (70) previously found that METTL14 expression is decreased in GC tissue samples, which is associated with poorer survival (70). Using methylation-RNA immunoprecipitation, Fan *et al* (70) showed that METTL14 can mediate the m6A modification of hsa_circ_0007612, also known as circular RNA (circ) origin recognition complex 5 (ORC5). Further investigations revealed that the downregulation of METTL14 lead to the upregulation of circORC5 expression. This increase in circORC5 expression then counteracted the inhibitory effects of miR-30c-23p on AKT1 substrate 1 and eIF4B, which increased the proliferation and invasion of GC cells (70). In addition, another study previously found that m6A modification of the phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP*) mRNA can be regulated by METTL14 in GC cells, where METTL14 correlated positively with LHPP with significance. Increasing the expression of *LHPP* was found to effectively inhibit the proliferation, invasion and migration of GC both *in vitro* and *in vivo* (71). LHPP overexpression can also inhibit the Wnt signaling pathway, which consequently inhibits the phosphorylation of GSK-3β and aerobic glycolysis in GC cells (71). Jin *et al* (72) reported that ibuprofen treatment can promote the expression of METTL3 and METTL14 in GC cells. METTL3 and METTL14 can also promote p53 translation, which in turn epigenetically increases p75 neurotrophin receptor (p75NTR) expression (72). p75NTR is considered to be a potential tumor suppressor that is associated with proliferation inhibition (72). Therefore, p75NTR may prove to be promising novel therapeutic target in the future.

The majority of research findings to date appear to suggest *METTL14* to be a tumor suppressor in GC (67-72). However, data suggesting that *METTL14* can function as an oncogene also exist. Hu and Ji (73) reported that METTL14-mediated m6A modification can upregulate *long intergenic non-coding RNA 01320* expression, which promoted the proliferation, migration and invasion of GC cells by increasing the expression of miR-495-5p whilst decreasing that of RAB19 (73).

Liver cancer. HCC is the fourth leading cause of cancer-related mortality worldwide, accounting for >80% of all cases of primary liver cancer (74,75). In total, 6% of China's population

Table I. Roles of METTL14 in digestive system tumors.

Cancer	Target	Role	Impact on the target	Mechanism	Functions in cancer	(Refs.)
Gastric cancer	Wnt/PI3K/Akt	Tumor suppressor	Knockdown of METTL14 activates Wnt and PI3K-Akt signaling	Regulate Wnt and PI3K/Akt signaling	Proliferation and invasion	(67)
	PI3K/AKT/mTOR	Tumor suppressor	Knockdown of METTL14 increases the phosphorylation levels of PI3K, AKT and mTOR	Regulate the PI3K/AKT/mTOR pathway	Proliferation, migration, and invasion	(68)
	PTEN	Tumor suppressor	Overexpression of METTL14 increases the expression of PTEN	Stabilized PTEN mRNA	Growth and metastasis	(69)
	CircORC5	Tumor suppressor	Knockdown of METTL14 increases the protein expression of circORC5	Regulate miR-30c-2-3p/AKT1 substrate 1 axis	Growth and invasion	(70)
	LHPP	Tumor suppressor	Knockdown of METTL14 decreases the expression of LHPP	Mediate HIF1A to inhibit glycolysis	Glycolysis, proliferation, invasion, and metastasis	(71)
	p75NTR	Tumor suppressor	Overexpression of METTL14 increases the expression of p75NTR	Ibuprofen increased m6A-p53 expression	Growth	(72)
	LINC01320	Oncogene	Overexpression of METTL14 increases the expression of LINC01320	Regulate the miR-495-5p/RAB19 axis	Proliferation, migration, and invasion	(73)
Liver cancer	miR-126	Tumor suppressor	Overexpression of METTL14 increases the expression of miR-126	Interact with the microprocessor protein DiGeorge syndrome critical region 8	Metastasis	(79)
	p53	Tumor suppressor	Knockdown of METTL14 decreases the p53 translation	Fusaric acid decreased p53 expression	-	(81)
	EGFR	Tumor suppressor	Knockdown of METTL14 increases the phosphorylation of EGFR	Modulate EGFR/PI3K/AKT signaling pathway	Migration, invasion, and EMT	(82)
	HNF3γ	Tumor suppressor	Knockdown of METTL14 decreases the expression of HNF3γ	Transactivation of OATP1B1 and OATP1B3 expression	Dedifferentiation and sorafenib resistance	(83)
	USP48	Tumor suppressor	Overexpression of METTL14 increases the expression of USP48	Regulate the Sirtuin 6 signaling pathway	Glycolysis and malignancy	(84)
	SLC7A11	Tumor suppressor	Knockdown of METTL14 increases the expression of SLC7A11	HIF-1α/METTL14/YTH DF2/SLC7A11 axis	Ferroptosis of hepatocellular carcinoma	(85)
	ACLY/SCD1	Oncogene	Overexpression of METTL14 increases the expression of ACLY/SCD1	N/A	Fatty acid synthase expression	(86)
	MIR155HG	Oncogene	Overexpression of METTL14 increases the expression of MIR155HG	Regulate programmed death-ligand 1 expression via miR-223-3p/STAT1 axis	Immune escape	(87)

Table I. Continued.

Cancer	Target	Role	Impact on the target	Mechanism	Functions in cancer	(Refs.)
	ARHGAP5-AS1	Oncogene	Knockdown of METTL14 decreases the expression of ARHGAP5-AS1	Promote translation of vimentin and RAC1 activate the ERK pathway	Invasion and metastasis	(88)
	CircFUT8	Oncogene	Overexpression of METTL14 increases the m6A level of CircFUT8	Regulate the circFUT8/miR-552-3p/charged multivesicular body protein 4B pathway	Growth	(89)
Colorectal cancer	ANKLE1	Tumor suppressor	Knockdown of METTL14 decreases the expression of ANKLE1	Recognized by YTHDF1	Proliferation and colony formation	(92)
	LncRNA XIST	Tumor suppressor	Knockdown of METTL14 increases the expression of LncRNA XIST	YTHDF2 mediate the degradation of XIST	Proliferation and metastasis	(93)
	SOX4	Tumor suppressor	Overexpression of METTL14 decreases the expression of SOX4	SOX4-mediated EMT process and PI3K/Akt signals	Migration, invasion, and metastasis	(94)
	KLF4	Tumor suppressor	Knockdown of METTL14 decreases the expression of KLF4	MethylCpG-binding protein 2 interacted with METTL14	Migration and invasion	(95)
	ARRDC4	Tumor suppressor	Overexpression of METTL14 decreases the expression of ARRDC4	Transcription factor 4/Hu antigen receptor/METTL14/ YHTDF2/ARRDC4/ zinc finger E-box binding homeobox 1 axis	Metastasis	(96)
	STAT1/IRF1	Tumor suppressor	Knockdown of METTL14 promotes the STAT1/IRF1 signaling	Promote IFN-γ/ STAT1/IRF1 signaling via YTHDF2	Immune responses to anti-PD-1 therapy	(97)
	EbI3	Tumor suppressor	Knockdown of METTL14 increases the expression of EbI3	Trigger a shift of intratumoral CD8+ T cells toward a dysfunctional state	Growth and impedes CD8+ T cell infiltration	(98)
	miR-149-3p	Tumor suppressor	Knockdown of METTL14 decreases the expression of miR-149-3p	PHD finger protein 5A transactivated superoxide dismutase 2 through regulating lysine acetyltransferase 2A mRNA alternative splicing by enterotoxigenic bacteroides fragilis	Inflammation and malignancy	(99)
	PHLDB2	Oncogene	Overexpression of METTL14 increases the expression of PHLDB2	Stabilize EGFR and promotes its nuclear translocation	Cetuximab resistance	(100)
Pancreatic cancer	PERP	Oncogene	Overexpression of METTL14 decreases the expression of PERP	Increase PERP mRNA turnover	Proliferation and migration	(104)

Table I. Continued.

Cancer	Target	Role	Impact on the target	Mechanism	Functions in cancer	(Refs.)
	miR-380-3p	Oncogene	Knockdown of METTL14 decreases the expression of miR-380-3p	miR-380-3p/ PTEN/Akt pathway	Proliferation, EMT and tumorigenesis	(105)
	AMPKα/ ERK/mTOR	Oncogene	Knockdown of METTL14 activates AMPKα/ERK/ mTOR signaling	Enhance apoptosis and autophagy	Cisplatin resistance	(106)
	CDA	Oncogene	Overexpression of METTL14 increases the expression of CDA	p65 targeted the promoter region of METTL14	Gemcitabine resistance	(108)
	PIK3CB	Tumor suppressor	Overexpression of PIK3CB decreases the expression of METTL14	Activate AKT signaling pathway	Proliferation and invasion	(109)
	CLK1/Serine/ arginine-rich splicing factor 5	Tumor suppressor	Overexpression of CLK1 increases the m6A level of METTL14	Control the exon skipping of METTL14 and Cyclin L2	Proliferation and metastasis	(110)
Cholangiocarcinoma	STIM2	Tumor suppressor	Knockdown of METTL14 decreases the expression of STIM2	STIM2-keratin 8 regulatory paradigm	Metastasis	(111)

METTL, methyltransferase-like; circ, circular RNA; Orc, origin recognition complex 5; LHPP, phospholysine phosphohistidine inorganic pyrophosphate phosphatase; HIF1α, Hypoxia-inducible factor 1α; p75 NTR, p75 neurotrophin receptor; miR, microRNA; LINC, long intergenic non-coding RNA; HNF3γ, hepatocyte nuclear factor 3γ; OATP, solute carrier organic anion transporter family member; USP48, ubiquitin-specific peptidase 48; SLC7A11, solute carrier family 7, member 11; YTHD, YTH domain-containing/family protein; ACLY, ATP citrate lyase; SCD1, Stearoyl-CoA 9-desaturase; MIR155HG, miR-155 host gene; ARHGAP5-AS1, rho GTPase-activating protein 5-antisense 1; FUT8, fucosyltransferase 8; ANKLE1, LEM domain-containing protein 1; XIST, X-inactive specific transcript; EMT, epithelial-mesenchymal transition; IRF1, IFN regulatory factor 1; KLF4, Kruppel-like factor 4; EbI3, Epstein-Barr virus-induced protein 3; PHLDB2, pleckstrin homology-like domain family B member 2; ARRDC4, arrestin Domain-Containing 4; PERP, p53 effector related to peripheral myelin protein 22; CDA, Cytidine Deaminase; PIK3B, PI3K catalytic subunit; CLK1, Cell division cycle 2-like kinase 1; STIM2, stromal interaction molecule 2.

is affected by hepatitis B infection and/or HCC (76). The low 5-year survival and high mortality rates for HCC are largely due to metastasis, poor response to chemotherapy and frequent postoperative recurrence (77). Epigenetic studies are therefore important for the discovery of novel therapeutic targets for HCC.

Zhou *et al* (78) previously found that METTL14 expression is significantly lower in HCC tissues, which is an independent prognostic factor for overall postoperative survival and tumor-free survival (78). Ma *et al* (79) reported that METTL14 can regulate the m6A modification of miR-126 by interacting with the microprocessor protein, DiGeorge syndrome critical region 8 (79). Functionally, miR-126 expression is significantly reduced in HCC cells, the overexpression of which was found to inhibit the metastatic effect of METTL14-deficiency *in vitro* (79). In HCC, expression of the tumor suppressor p53 can also be regulated by METTL14 (80). A study previously found that fusaric acid (FA) can reduce the expression of METTL14 to epigenetically suppress p53 expression in the HepG2 cell line (81). In addition, using RNA-sequencing and m6A-sequencing, Shi e*t al* (82) found that *EGFR* is a downstream target of METTL14 in HCC. METTL14 expression is downregulated in HCC, which can activate the phosphorylation of EGFR and subsequent PI3K/AKT signaling to promote migration, invasion and EMT (82). METTL14 can indirectly promote sorafenib resistance by decreasing hepatocyte nuclear factor 3γ (HNF3γ) mRNA expression through m6A. HNF3γ can promote hepatic cancer stem cell differentiation into HCC cells, inhibit the proliferation of HCC and sensitize HCC cells to sorafenib-induced and apoptosis by activating the expression of sorafenib membrane transporters solute carrier organic anion transporter family member (OATP)1B1 and OATP1B3 (83). Mechanistically, the increased *HNF3γ* mRNA stability were likely to be mediated through IGF2BPs (83). In addition, Du *et al* (84) demonstrated that m6A modification induced by METTL14 increased the stability of ubiquitin-specific peptidase 48 (*USP48*) mRNA to upregulate its expression. *USP48* then stabilized sirtuin 6 proteins to prevent metabolic reprogramming from mitochondrial respiration toward aerobic glycolysis, then enhanced glycolytic homeostasis and inhibited tumor growth (84). Another study previously found that ferroptosis was blocked in HCC cells under hypoxic conditions due to the inhibition of METTL14 by hypoxia-inducible factor 1-alpha (HIF-1α) (85). Further investigation revealed that METTL14 can negatively regulate the expression of solute carrier family 7,

member 11 (SLC7A11) through the YTHDF2-dependent pathway. Downregulation of SLC7A11 resulted in ferroptosis, inhibiting the progression of HCC (85). Therefore, the HIF-1α/METTL14/YTHDF2/SLC7A11 axis may provide a basis for the treatment design of HCC.

However, at present there is no unanimous consensus on the role of METTL14 in liver cancer. A number of studies have suggested that *METTL14* can serve as an oncogene in liver cancer. Yang *et al* (86) found that the levels of METTL14 and METTL3 expression are higher in HCC cell lines and human HCC tissue samples (86). Overexpression of METTL14 directly increased m6A levels on the ATP citrate lyase and stearyl-CoA desaturase 1 mRNA transcripts in HCC cells. This enhanced the production of triglycerides and cholesterol, in addition to the accumulation of lipid droplets in HCC, leading to HCC proliferation, angiogenesis and the HCC progression (86). The pathogenesis of HCC is associated with pathogen-associated molecular patterns, where lipopolysaccharides (LPS) can enter the liver through the entero-liver axis to promote the progression of HCC. LPS may be one of the regulators upregulated by METTL14 in HCC (87). LPS can upregulate METTL14 to enhance the m6A methylation level of miR-155 host gene (MIR155HG), which then stabilizes the MIR155HG mRNA through the 'reader' protein abnormal vision-like 1. In addition, LPS can increase the expression of programmed death-ligand 1 (PD-L1) by upregulating the expression of miR-155HG (87). In addition, overexpression of MIR155HG can inhibit the expression of miR-223-3p, which then increases the expression of STAT1 and the expression of PD-L1 in HCC. Based on the m6A-sequencing data from HCC cells, Liu *et al* (88) previously observed that *rho GTPase-activating protein 5* (*ARHGAP5*)*-antisense (AS)1* is the long non-coding RNA (lncRNA) showing the highest level of m6A modification. Silencing METTL14 expression was found to reduce m6A and *ARHGAP5-AS1* expression (88). Furthermore, inhibition of cold shock domain-containing E1 degradation by *ARHGAP5-AS1* was found to promote the translation of vimentin and Ras-related C3 botulinum toxin substrate 1 (RAC1) to activate the ERK pathway in HCC. ERK activation then in turn promoted HCC cell proliferation, migration and invasion (88). Another previous study revealed that miR-628-5p in the exosomes secreted by M_1 macrophages can inhibit expression of METTL14 in HCCs following transportation (89). The m6A modification of *Circ-fucosyltransferase 8 (circFUT8)* is positively regulated by METTL14, where CircFUT8 is upregulated in HCC cells. CircFUT8 overexpression can inhibit HCC apoptosis whilst promoting cell proliferation through the miR-552-3p/charged multivesicular body protein 4B pathway (89).

Colorectal cancer (CRC). CRC is one of the most common malignancies in adults, ranking third in the cases of cancer-related mortality worldwide (90) in 2020. The mortality rate in patients with CRC remains high largely due to high rates of metastasis and recurrence (65,91). Studying epigenetics can provide insight into the mechanisms regulating the progression of colorectal cancer.

LEM domain-containing protein 1 (*ANKLE1*) is a CRC susceptibility gene, where *ANKLE1* m6A methylation is catalyzed by the METTL3/METTL14/WTAP complex and then recognized by YTHDF1 (92). Presence of the rs8100241(A) allele has been documented to increase *ANKLE1* m6A methylation (92). Methylated *ANKLE1* inhibits tumor growth, maintains genomic stability and reduces CRC risk (92). Yang *et al* (93) found that the downregulation of METTL14 expression is associated with poorer prognosis in patients with CRC (93). LncRNA X-inactive specific transcript (*XIST*) is a downstream target of METTL14, where knocking down METTL14 expression was found to reduce the level of m6A modification and enhance XIST expression in CRC cells (93). METTL14 can also mediate *XIST* degradation through the YTHDF2-dependent m6A modification pathway. *XIST* degradation suppresses the proliferation, invasion and migration of CRC cells (93). Another study found that the demethylation of histone H3 in the *METTL14* gene promoter region mediated by lysine-specific histone demethylase 5C (KDM5C) can inhibit *METTL14* transcription (94). In addition, METTL14 has been shown to promote the degradation of SOX4 mRNA through a YTHDF2-dependent pathway (94). This suppression of SOX4 in turn inhibits the migration and invasion of CRC cells, since SOX4 can normally activate the EMT process and PI3K/Akt signaling in CRC cells (94). MethylCpG-binding protein 2 (MeCP 2) was also found to inhibit METTL14 in CRC cells (95). Specifically, MeCP2 expression was found to be upregulated in CRC, whilst that of METTL14 was downregulated. MeCP2 and METTL14 can interact and specifically recognize Kruppel-like factor 4 (KLF4) mRNA through the 'reader' protein IGF2BP2 (95). The tumor suppressor KLF4 has been previously demonstrated to inhibit the migration and invasion of CRC. Binding of MeCP2 and METTL14 can inhibit the translation of the KLF4 mRNA to promote the metastasis of CRC (95). Wang *et al* (96) found that Hu antigen receptor (HuR) can inhibit METTL14 mRNA expression by binding to its promoter in CRC. Transcription factor 4 (TCF4) deficiency was also found to increase the ubiquitination of METTL14, thereby promoting its degradation. METTL14 can itself inhibit downstream arrestin domain-containing 4/zinc finger E-box binding homeobox 1 (ZEB1) signaling through YTHDF2-dependent m6A modification, which prevents colorectal cancer metastasis (96).

In addition to demonstrating its function in CRC proliferation, invasion and migration, a number of studies have also reported METTL14 to regulate other biological processes. Wang *et al* (97) found that decreased expression of METTL3 and METTL14 can increase IFN-γ/STAT1/IFN regulatory factor 1 (IRF1) signaling by stabilizing IFN-γ, C-X-C motif chemokine ligand (CXCL)9 and CXCL10 secreted by tumor-infiltrating CD8+ cytotoxic T cells in the tumor microenvironment. This then increases the IFN content in the tumor microenvironment and increase the recruitment of immune cells (97). IFN-γ/STAT1/IRF1 signaling may provide insight into the mechanism of poor response to immune checkpoint inhibitor (ICIs) therapy in mismatch-repair-proficient or microsatellite low instability CRC (97). Another recent study found that the downregulation of METTL14 m6A methylation in C1q+ tumor-associated macrophages can increase the levels of the cytokine IL-35 subunit Epstein-Barr virus-induced protein 3 (EBI3) mRNA transcript. This EBI3 elevation in turn promoted CD8+ T cell differentiation into a dysfunctional state, which have weaker proliferative capabilities and reduced

response potency to tumors, leading to CRC progression (98). Consistent with the findings in liver cancer, METTL14 was also found to regulate miRNA expression by modifying pri-miRNA splicing in CRC (99). Enterotoxigenic bacteroides fragilis in the gut flora was shown to positively regulate the expression of pri-miR-149 through METTL14-mediated m6A methylation in CRC (99). Reducing miR-149-3p expression in the plasma exosomes of patients with CRC was found to increase proliferation and induce an inflammatory response in CRC cells (99). Functionally, miR-149-3p increases the expression of the *PHD finger protein 5A* gene downstream to stabilize the splicing factor 3b complex and transactivate superoxide dismutase 2 (SOD2), by regulating lysine acetyltransferase 2A mRNA alternative splicing and increase the expression of SOD2 mRNA, to induce colorectal carcinogenesis (99). Another previous study documented that oxidative stress induced by chemotherapeutic drugs can upregulate the methylation of *pleckstrin homology-like domain family B member 2* (*PHLDB2)* by METTL14 in CRC, which increases protein expression (100). Nuclear EGFR is a transcriptional cofactor that can function to regulate gene expression and promote DNA repair (100). Increased PHLDB2 expression can stabilize EGFR and promotes its nuclear translocation, which promotes cetuximab resistance (100). Rab11A is a common EGFR recycling protein that facilitate EGFR translocation back to the cell membrane, the mechanism by which PHLDB2 can promote the nuclear translocation of EGFR may be mediated by reducing the binding affinity between EGFR and Rab11A (100).

Pancreatic cancer (PC). PC is one of the most aggressive malignancies, with a 5-year mortality rate of ~95% after diagnosis (65). Additionally, majority of patients with PC do not survive for >7 years following surgical treatment (101,102). For patients with advanced pancreatic cancer, chemotherapy or chemo-radiotherapy is typically applied, but chemotherapy resistance frequently leads to worse prognosis (103). Unlike other digestive system malignancies, existing evidence actually suggest *METTL14* to be an oncogene in PC.

A previous study showed that the overexpression of METTL14 in PC cells can increase methylation of *p53 effector related to peripheral myelin protein 22* (*PERP*) downstream. *PERP* mRNA methylation reduces PERP protein expression, which promotes PC cell proliferation and migration (104). Decreased m6A modification of METTL3 and METTL14 inhibits the expression of miR-380-3p in PC cells, which was demonstrated by Jiang *et al* (105). By contrast, the expression level of miR-380-3p was previously found to be significantly higher in PC tissues and cells. Further experiments found that miR-380-3p can promote PC cell proliferation and tumorigenesis through Akt signaling, EMT by suppressing PTEN expression (105). In addition, drug-resistant PC tissues tend to express higher levels of METTL14 according to Kong *et al* (106). Accordingly, knocking down METTL14 expression was found to enhance both apoptosis and autophagy in PC cells through activating 5'AMP-activated protein kinase (AMPKα) and ERK1/2 signaling to restrain mTOR signaling, allowing for increased sensitivity to cisplatin. Cisplatin is essential therapeutic agent for the treatment of patients with *breast cancer gene (BRCA)1/2* or *partner and localizer of BRCA2* mutations (107). Therefore, these findings may provide guidance for chemotherapy regimen selection in patients with PC. Furthermore, another study found that METTL14 can promote resistance to gemcitabine in PC cells, which can be reversed with *METTL14* knockdown (108). METTL14 expression was observed to be upregulated in gemcitabine-resistant human PC cells, where increased METTL14 expression was also found after gemcitabine treatment. Further studies then revealed that the NF-κB transcription factor p65 can target the promoter region of *METTL14* to positively its mRNA and protein expression. This in turn upregulated the expression of cytidine deaminase to inactivate gemcitabine.

Contrary to the aforementioned findings, certain studies have also reported that *METTL14* can function as a tumor suppressor in PC. PI3K catalytic subunit (PIK3CB) expression is frequently increased in PTEN-deficient PC cells (109). PIK3CB overexpression was found to reduce the expression of components in the METTL3/METTL14/WTAP complex and activate AKT signaling, which enhanced the proliferative and migratory capacity of PC cells. Cell division cycle 2-like kinase 1 (CLK1) was also found to be upregulated in PC tissues, which enhances the phosphorylation of serine/arginine-rich splicing factor 5 (SRSF5) to suppress METTL14 exon 10 skipping. METTL14 exon 10 skipping enhances the degree of m6A modification on its gene. CLK1 can also enhance PC cell proliferation, migration and invasion by decreasing the m6A level of METTL14, in addition to promoting cyclin L2 exon 6.3 skipping (110). However, the downstream regulatory mechanism of METTL14 remains unclear.

Other cancers. In cholangiocarcinoma (CCA), lower expression levels of stromal interaction molecule 2 (STIM2) is associated with poor prognosis (111). m6A modification mediated by METTL14 and YTHDC2 was found to decrease the expression of *STIM2* mRNA (111). Consequently, knockdown of *STIM2* can increase keratin 8 (KRT8) expression to facilitate extrahepatic CCA metastasis (111).

5. Research advances in bioinformatics

The Cancer Genome Atlas (TCGA) is a useful tool for determining DNA, RNA and protein expression levels, in addition to exploring gene function, in a variety of cancers (112). Preliminary understanding can first be obtained, which can then be verified using experimental data (112). This section summarizes the results of m6A-related studies obtained by bioinformatics analysis alone.

The majority of the bioinformatics studies performed focused on the expression levels of METTL14 and their prognostic value. Zhou *et al* (78) found that METTL14 expression in HCC tissues is significantly lower compared with those in adjacent tissues. Furthermore, METTL14 expression in HCC tissues is associated with tumor size and tumor-node-metastasis (TNM) stage in patients with HCC. Lower expression levels of METTL14 in HCC tissues were significantly associated with poorer prognosis, with the overall survival and tumor-free survival rates being significantly shortened. Liu *et al* (56) also showed that METTL14 expression is lower in HCC tissues and associated with poorer prognosis. By contrast, the opposite trend was observed in terms of the prognostic values of METTL3 in HCC (56). Kong *et al* (113) found that

Table II. Upstream mechanism of METTL14.

Cancer	Upstream regulator	Function	Regulation mechanism	(Refs.)
Liver cancer	Fusaric acid	Inhibit the m6A level of METTL14	N/A	(81)
	Hypoxia-inducible factor 1α	Inhibit the expression of METTL14	Under hypoxic conditions	(85)
	Lipopolysacharide	Enhance the expression of METTL14	N/A	(87)
	miR-628-5p	Inhibit the expression of METTL14	M1-exo transfer miR-628-5p to HCC cell	(89)
Colorectal cancer	Lysine-specific histone demethylase 5C	Inhibit the transcription of METTL14	Demethylation of histone H3K4me3 in the promoter region	(94)
	MethylCpG-binding protein 2	Inhibit the m6A level of METTL14	Affect the interaction between METTL3 and METTL14	(95)
	Hu antigen receptor	Inhibit the expression of METTL14	Binding to the promoter	(96)
	Transcription factor 4	Enhance the expression of METTL14	Inhibits ubiquitination of METTL14	(96)
Pancreatic cancer	Cell division cycle 2-like kinase 1	Enhance the m6A level of METTL14	Inhibited METTL14$^{exon\ 10}$ skipping	(110)

METTL, methyltransferase-like; miR, microRNA.

the expression of METTL14 is upregulated in HCC tissues, but the downregulation of METTL14 is associated with poor prognosis (113), possibly due to lower levels of immune cell infiltration (113). Another study revealed that METTL14 may participate in the malignant progression of HCC by regulating the expression levels of cysteine sulfinic acid decarboxylase, glutamate-oxaloacetate transaminase 2 and suppressors of cytokine signaling 2 (114). The author used LASSO analysis to analyze a total of 124 prognostic genes in 307 TCGA samples to find real hub genes that are associated with patient prognosis, but the specific mechanism needs to be verified by further experiments (114). The results of the aforementioned analyses suggest that METTL14 is upregulated in HCC and inversely associated with clinical prognosis. Xu *et al* (115) previously suggested that METTL14 expression is upregulated in PC, which displayed a U-shaped association with clinical stage. Specifically, expression in stages I and IV was higher compared with that at stages II and III. Additionally, METTL14 expression is negatively associated with the T phase (115). Similarly, another previous analysis by Zhang *et al* (116) revealed that METTL14 is highly expressed in PC tissues. Additionally, two studies on rectal cancer found that METTL14 expression is associated with worse prognosis (117,118). In addition, METTL14 expression was positively correlated with the degree of immune cell infiltration, as found by Cai *et al* (117). In GC, Xu *et al* (119) found that lower METTL14 expression significantly correlated with the expression levels of PD-L1 and PD-1 (119). Using LASSO regression analysis, a study on esophageal cancer (ESCA) found that METTL14 expression can be used to predict overall survival in patients with ESCA (120).

6. Potential research direction for METTL14 and digestive system cancers

As a methyltransferase, METTL14 can mediate m6A methylation to regulate various physiological processes in malignancies, such as proliferation, invasion, metastasis and drug resistance (10). In addition, METTL14 expression can be used as a marker for the diagnosis and prognosis of digestive system tumors. Using bioinformatics, several studies have analyzed the expression profile of METTL14 in digestive system cancers and developed various prognostic risk models (114,115). Further validation is required to explore the specificity and sensitivity of METTL14 as a marker. METTL14 expression may also confer benefits for predicting efficacy. The role of METTL14 in cisplatin and gemcitabine resistance in PC suggests that it can be used for predicting chemotherapy outcome (108). Wang *et al* (97) previously found that METTL14 can regulate the response of CRC cells to immunotherapy, suggesting that METTL14 can enhance the effectiveness of immunotherapy, either when combined with other drugs or as a potential independent therapeutic target (97).

METTL14 mediate different regulatory roles in different tumors. In GC and CRC, the majority of the evidence suggest that METTL14 serves as a tumor suppressor, whereas in PC they suggest METTL14 to be an oncogene. In HCC, the role of METTL14 remains controversial. Whether *METTL14* itself is an oncogene or tumor suppressor remains a matter of debate. In addition, the mechanism underlying the regulation of METTL14 remain elusive. A study did previously find that the SUMOylation of METTL3 significantly inhibited its m6A methyltransferase activity in NSCLC, resulting in reduced m6A levels. However, this did not affect METTL14 stability, localization or its interaction with WTAP (121).

In terms of the possible upstream mechanisms that can regulate METTL14 expression, binding to its promoters and subsequent inhibition of METT14 transcription or direct regulation of METTL14 mRNA expression has been considered. Upstream regulators include RBPs, transcription factors, exosomes from M_1 macrophages and endotoxins produced by the gut flora (Table II). In liver cancer, FA

can reduce the m6A of METTL14 in HepG2 cells to subsequently inhibit p53 gene expression (81). The transcription factor HIF-1α can also inhibit METTL14 expression and promote the development of HCC under hypoxic conditions (85). In addition, LPS treatment was found to increase the expression of METTL14 in Huh7 cells whilst increasing the m6A methylation level of MIR155HG (87). Exosomes of M_1 macrophages inhibited METTL14 expression by transferring miR-628-5p to HCC cells, which inhibited the m6A modification of circFUT8 (89). In CRC, KDM5C-mediated demethylation of histone H3K4me3 in the promoter region inhibited METTL14 transcription, which may account for the reduction of METTL14 expression found in CRC (94). MeCP2 was also found to inhibit the m6A methylation of METTL14 in CRC cells, mechanistically due to MeCP2 competitively disrupting the interaction between METTL3 and METTL14 (95). In addition, the RBP HuR can inhibit METTL14 mRNA expression by binding to its promoter (96), whereas TCF4 deficiency significantly increased the ubiquitination level of METTL14 and promoted its protein degradation (96). In PC, CLK1 enhanced the phosphorylation of SRSF5 on Ser-250, which inhibited METTL14 exon 10 skipping and increased the level of m6A modification (110). Therefore, the regulatory mechanism of METTL14 function in the individual tumor types must be strictly defined. In addition, the mechanism of action of the METTL3/METTL14 complex remains unclear. In particularly, whether the two function allosterically or synergistically remain unknown. A previous study in HCC reported that the expression and function profiles of the two are distinct and do not share common pathways downstream (56).

The PI3K/AKT signaling pathway is frequently found to be associated with cancer development, metastasis and EMT. Previous studies in LC, GC and CRC have confirmed that the PI3K/AKT signaling pathway is a downstream regulatory pathway of METTL14 (67,68,82,94). HIF-1α can inhibit the expression of METTL14 in HCC, but HIF-1α can be regulated by METTL14 in GC as one of its downstream targets (71,85). The EGFR signaling pathway was found to serve downstream of METTL14 in LC and CRC (82,100), whereas the ERK signaling pathway was found to serve downstream of METTL14 in HCC and PC (88,107). In conclusion, the mechanism of regulation by METTL14 in digestive system malignancies is one of the most important directions for future research.

Anti-angiogenic therapy is an important modality for digestive system tumor treatment (122). Due to the low mutation rate of anti-angiogenic genes in CRC (122), epigenetic modifications may provide a more appropriate target for blocking tumor angiogenesis. The role of m6A regulation in tumor angiogenesis is currently a topic of intense research. Chen *et al* (123) previously found that METTL14-mediated m6A methylation can increase *TNF receptor-associated factor* RNA stability and inhibit sunitinib-mediated anti-angiogenic effects in renal cancer cells (123). In addition, Wen *et al* (124) revealed that basic leucine zipper activating transcription factors-like transcription factor 2 (BATF2) expression is downregulated in tongue squamous cell carcinoma (TSCC). Downregulated BATF2 serves a role in promoting tumor growth, metastasis and angiogenesis (124). METTL14-mediated m6A modification was found to inhibit BATF2 mRNA expression and increase the expression of vascular endothelial growth factor A (124). The role of METTL14 in angiogenesis in digestive system tumors remains uncharacterized, exploring it would be of great clinical significance for patients with digestive system tumors in addition to providing a potential research direction.

In conclusion, the expression and role of METTL14 in different digestive system cancers remain controversial. In particular, the regulatory mechanism of METTL14 require further study. Although METTL14 has been demonstrated to serve an important role in digestive system tumors, its implications for clinical application also requires further investigation.

7. Conclusion

In summary, METTL14 serves diverse roles in digestive system cancers and has diagnostic and therapeutic potential. Further exploration of the regulatory mechanisms of METTL14 is anticipated, which is expected to accelerate their incorporation into clinical treatment.

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Authors' contributions

JXH and HSL contributed to conception and design. JXH and CW contributed to literature search. JXH contributed to manuscript writing. QS and BWC approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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