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Review Article

WTAP-mediated m6A regulation in digestive system cancers: from molecular mechanisms to therapeutic strategies

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Abstract: Epigenetic modifications, particularly RNA methylation, play a crucial role in cancer progression, and N6-methyladenosine (m6A) is the most prevalent mRNA modification in eukaryotes. Wilms tumor 1-associated protein (WTAP), a key component of the m6A methyltransferase complex (MTC), regulates m6A modification, influencing RNA stability, translation, and degradation. WTAP dysregulation has been implicated in various malignancies, with particularly significant roles observed across the digestive system cancers, including but not limited to esophageal, gastric, pancreatic, gallbladder, hepatocellular, and colorectal carcinomas. Overexpression of WTAP is frequently associated with poor prognosis, advanced tumor stages, and increased metastatic potential. This review highlights the multifaceted roles and regulatory network of WTAP in digestive system cancers (DSCs) progression, encompassing tumor cell proliferation, migration, invasion, drug resistance, and immune evasion. Targeting WTAP may offer novel therapeutic strategies for overcoming therapy resistance and improving clinical outcomes in digestive system malignancies. Future research should prioritize: (1) validation of these findings in larger, multicenter, and ethnically diverse patient cohorts; (2) comprehensive elucidation of the molecular mechanisms underlying WTAP-mediated regulation in cancer biology; and (3) systematic exploration of its functional consequences in tumor progression and therapy resistance.

Keywords: WTAP, m6A, digestive system malignancies, function, mechanisms

Introduction

Methylation is the most prevalent post-transcriptional RNA modification, involving N6-methyladenosine (m6A), N1-methyladenosine (m1A), 5-methylcytosine (m5C), and 7-methylguanosine (m7G) [1].

In 1974, m6A modification was first discovered in eukaryotic mRNAs [2], which has been identified as the most abundant form of mRNA modification in eukaryotes [3]. Recent genome-wide analyses have identified m6A modifications in approximately 7,000 protein-coding genes across mammalian species, highlighting its widespread regulatory potential [4]. m6A modifications usually occur on 'RRACH' RNA sequences (R=A or G; H=U, A or C) [5]. Functionally, m6A modifications are involved in multiple biological processes which contain precursor mRNA (pre-mRNA) splicing [6], mRNA translation [7], stability [8] and degradation. Extensive research has established the critical involvement of m6A modification in fundamental cancer biology processes, encompassing tumor cell proliferation, invasion, migration, differentiation, and apoptosis regulation [9].

The m6A modification process is dynamically regulated by three classes of regulatory proteins. To date, m6A regulators can be categorized into methyltransferases ('writers'), demethylases ('erasers'), and RNA-binding proteins ('readers').

The m6A writer machinery consists of multiple essential subunits, for example, methyltransferase-like 3 (METTL3), methyltransferase-like

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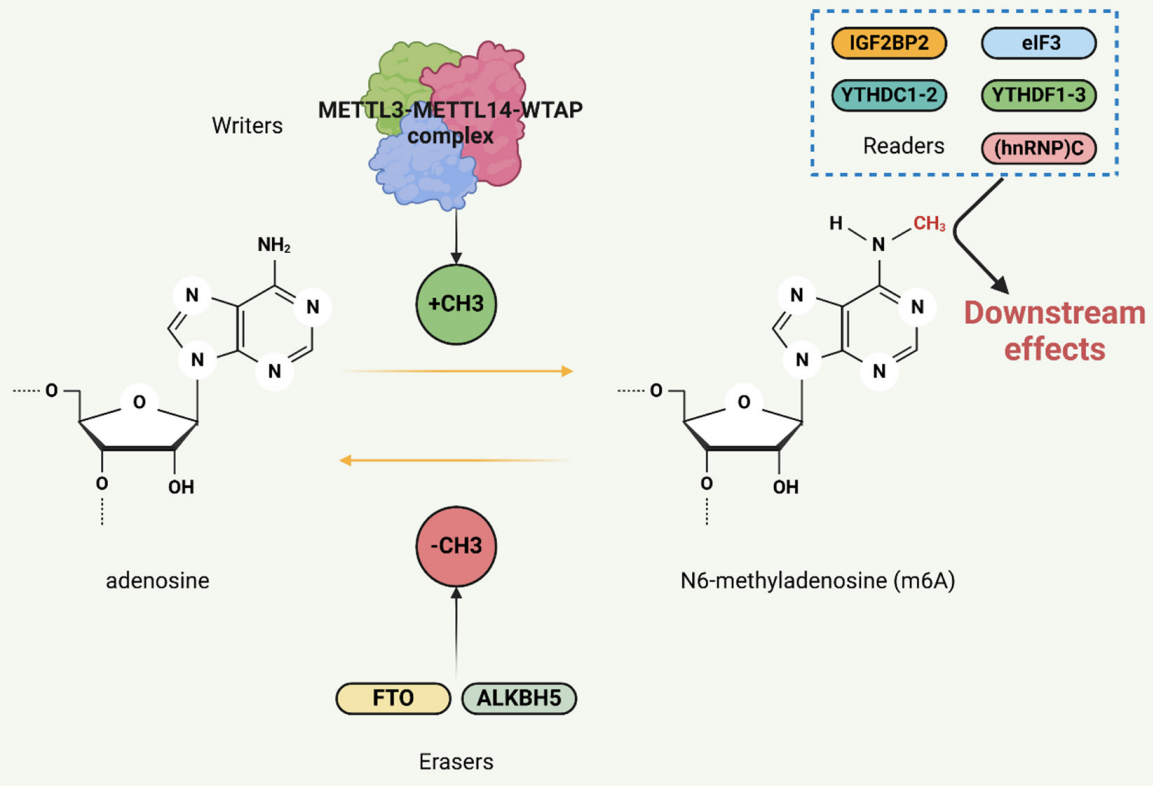

Figure 1. An introduction of m6A modification. m6A writers are methyltransferases (METTL3-METTL14-WTAP complex) that catalyze the addition of a methyl group to adenosine in RNA. m6A erasers (FTO and ALKBH5) are demethylase enzymes that remove methyl groups from m6A in RNA. m6A readers are proteins (the YTH domain family) that recognize and bind to m6A-modified RNA to exert biological functions. METTL, Methyltransferase-like; WTAP, Wilms tumor 1-associated protein; FTO, Fat mass and obesity-associated; ALKBH5, AlkB homolog 5; IGF2BP, Insulin-like growth factor-2 mRNA-binding proteins; eIF3, Eukaryotic initiation factor 3; YTHD, YTH domain-containing/family proteins; hnRNP, Heterogenous nuclear ribonucleoproteins.

14 (METTL14) and methyltransferase-like 16 (METTL16), along with regulatory components such as WTAP, RNA-binding motif protein 15 (RBM15) and Vir-like m6A methyltransferase (VIRMA). Previous studies have reported that METTL3, METTL14 and WTAP form the MTC that catalyzes m6A modification [10], which can be removed by m6A erasers, such as fat mass and obesity-associated protein (FTO) [11] and alkylation repair homolog protein 5 (ALKBH5) [12]. m6A erasers enable m6A modification to be a reversible process. Besides, m6A readers include YT521-B homology (YTH) domain-containing proteins, comprising two nuclear readers (YTHDC1-2) and three cytoplasmic readers (YTHDF1-3) [13], heterogeneous nuclear ribonucleoproteins (hnRNP) C [14], insulin-like growth factor-2 mRNA binding proteins (IGF2BP2) [15] and translation initiation factors eukaryotic initiation factor 3 (eIF3) [16] (**Figure 1**).

DSCs account for a large proportion of new-diagnosed cancer worldwide with a high mortality, which include esophageal carcinoma, gastric cancer, liver cancer, gallbladder cancer, pancreatic cancer and colorectal cancer [17]. To date, though there have been breakthroughs in cancer therapies as immune checkpoint inhibitors and molecularly targeted agents, clinical treatments of DSCs still present major clinical challenges due to therapeutic resistance and tumor heterogeneity. Targeting m6A modification may provide new insights into DSCs' treatments from the perspective of molecular mechanisms [18].

Overview of WTAP

WTAP is a WT1-associated nuclear protein which was first reported in 2000 and localizes throughout the nucleoplasm and co-localizes with splicing factors [19]. WTAP mediates m6A

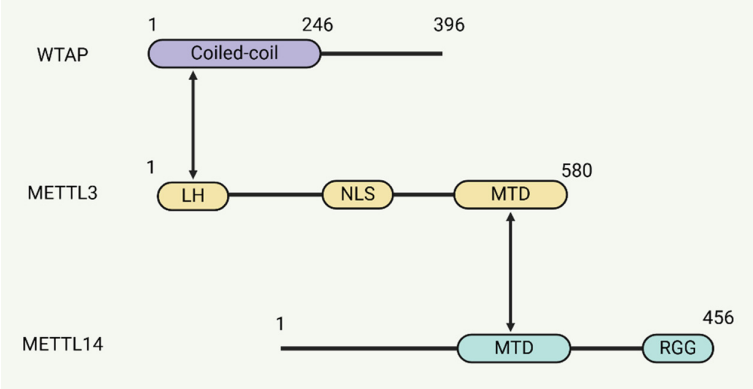

Figure 2. Interaction surfaces within the METTL3-METTL14-WTAP complex. The METTL3-METTL14-WTAP complex is the core writer of m6A RNA methylation. METTL3 is the catalytic subunit, METTL14 enhances substrate binding and stability, and WTAP (Wilms' tumor 1-associated protein) facilitates complex localization and recruitment to target RNAs. METTL3 and METTL14 form a heterodimeric complex that interacts with WTAP. The N-terminal coiled coil region of WTAP that contains 150 amino acids binds WTAP with METTL3 and the LH at the N terminus of METTL3. The interaction between METTL3 and METTL14 is facilitated by the MTD. LH, Leader helix; MTD, Methyltransferase domain.

modification by forming the methyltransferase complex with METTL3 and METTL14, enabling nuclear speckle translocation of these subunits [20]. Furthermore, WTAP regulates the recruitment of MTC to mRNA targets, without which the RNA-binding capacity of METTL3 is significantly weakened [21]. It has been reported that WTAP contains an extended N-terminal coiled coil region followed by a highly unstructured C-terminal part. The N-terminal 150 amino acids bind WTAP to METTL3 and the leader helix (LH) at the N terminus of METTL3 is necessary for the interaction between WTAP and METTL3, as well as the formation of the METTL3-METTL14-WTAP complex. The NLS (nuclear localization signals) of WTAP are in the N terminus, the sequence of which is PLPKKVRL [22] (**Figure 2**).

Wu *et al.* identified a series of transcription factors regulating WTAP expression and its functional roles in tumorigenesis, the binding sites of signal transducer and activator of transcription 1 (STAT1), forkhead box protein O1 (FOXO1), interferon regulatory factor 1 (IRF1), glucocorticoid receptor and peroxisome proliferator-activated receptor γ (PPARγ) binding sites were discovered in the promoter region of human WTAP gene [23]. At the transcriptional level, many molecular TTC22 was identified to interact with 60S ribosomal protein L4 (RPL4). Consequently, the binding of WTAP to RPL4 was enhanced, leading to increased stability and translation efficiency of WTAP mRNA [24]. Moreover, multiple molecules have been found to bind to WTAP mRNA to exert biological effects. For instance, an overabundance of Wilms Tumor 1 Associated Protein Pseudogene 1 (WTAPP1) RNA interacted with its protein-coding counterpart WTAP mRNA, and facilitated the recruitment of additional eIF3 translation initiation complexes, thereby enhancing WTAP translation [25]. Besides, carbonic anhydrase IV (CA4) was found to directly interact with WTAP, triggering its polyubiquitination-mediated protein degradation [26].

WTAP regulates diverse biological processes, including pre-mRNA splicing, cell cycle progression and differentiation, which are closely related to tumor growth and progression. For example, WTAP influences G1/S transition in renal cell carcinoma by regulating CDK2 mRNA stability via binding to its 3'-UTR [27, 28]. WTAP is critically involved in carcinogenesis across multiple systems, including hematopoietic, digestive, reproductive, urinary, and respiratory systems [29] (**Figure 3**).

Roles of WTAP in digestive system cancer

Recently, plenty of studies have reported the significance of WTAP in digestive system cancer. In this review, we will focus on the functions of WTAP, as well as its upstream regulators and downstream targets in digestive system malignancies. WTAP's roles across different cancers are summarized in **Table 1**. Furthermore, we will explore the prognostic values of WTAP as a potential therapeutic target.

Esophageal cancer (EC)

Nowadays, esophageal cancer has been reported to be the sixth cause of cancer-related death, the incidence of which has witnessed a drastic increase over the past few decades. Research has shown that the incidence of

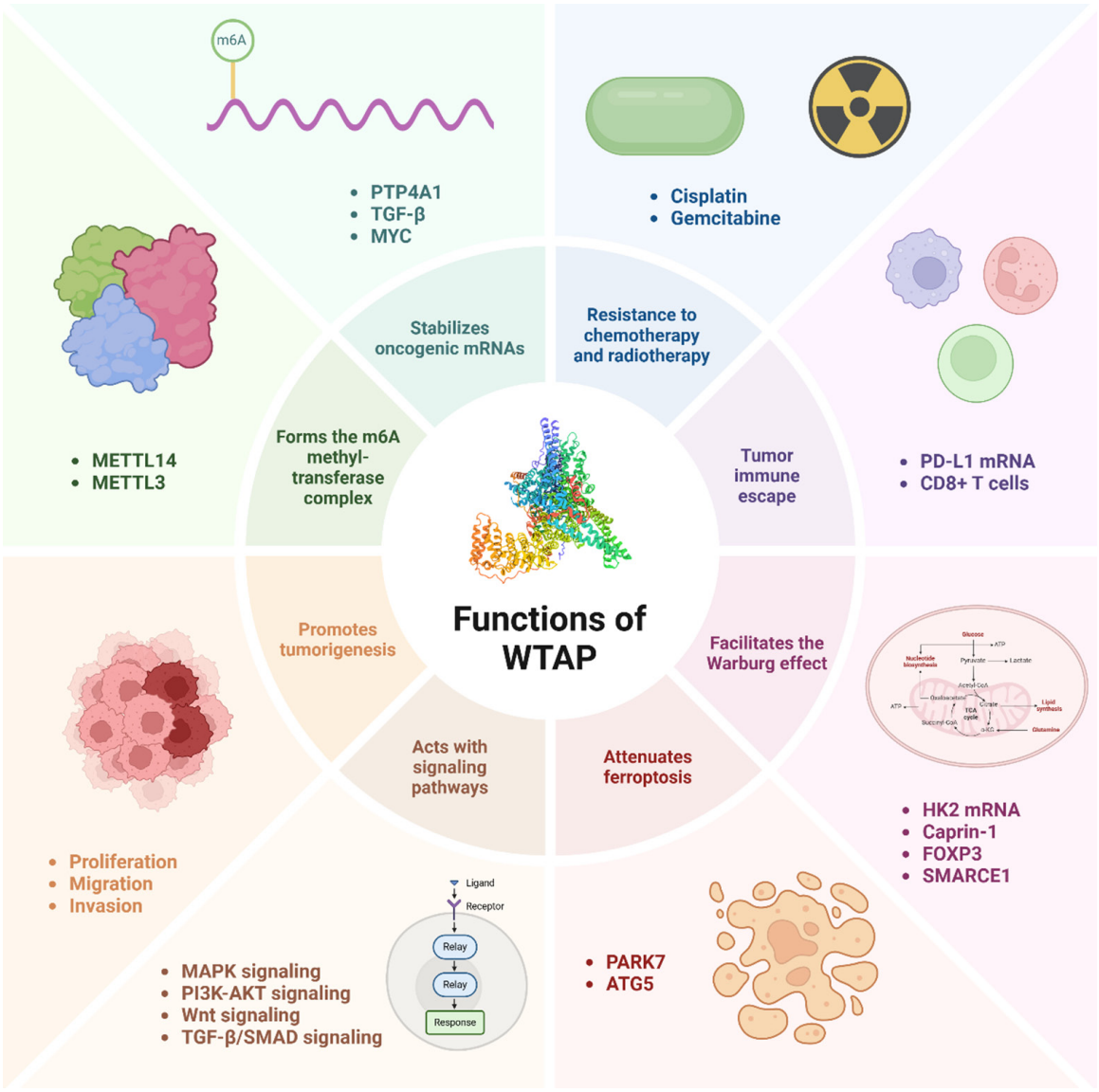

Figure 3. WTAP plays multifaceted roles in cancer biology and cellular processes. WTAP promotes tumor immune escape by modulating PD-L1 mRNA and CD8+ T cells, and it enhances resistance to chemotherapy and radiotherapy, including agents like cisplatin and gemcitabine. Additionally, WTAP facilitates the Warburg effect, a metabolic shift favoring glycolysis in cancer cells, and interacts with critical signaling pathways such as MAPK, PI3K-AKT, Wnt, and TGF-β/SMAD. It also attenuates ferroptosis, a form of cell death, and supports cancer cell proliferation, migration, and invasion. The function of WTAP is linked to various molecules, including HK2 mRNA, Caprin-1, FOXP3, and SMARCE1, highlighting its broad impact on cancer progression and cellular metabolism. PD-L1, Programmed cell death ligand 1; MAPK, Mitogen-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase; TGF-β, Transforming growth factor beta; SMAD, Sma and Mad related protein; FOXP3, Transcription factor forkhead box protein 3.

esophageal cancer is especially high in East Asia, eastern and southern Africa, and southern Europe [30].

Biological Role: It has been reported that the expression of WTAP is higher in EC and increased WTAP levels usually indicate advanced stages and shorter overall survival (OS) [31-33].

Besides, WTAP level is positively correlated with TNM stage and the higher expression of WTAP can promote lymph node metastasis in esophageal squamous cell carcinoma (ESCC) [34].

Mechanistic Insights: A Recent study identified Cyclin D1 (CCND1) as a potential downstream

Table 1. WTAP's roles across different cancers

Functional Category	Role of WTAP	Target of WTAP	Type of Cancer	Mechanism	Biological Function	References
Tumor Metabolism and Microenvironment Remodeling	Oncogene	HK2	Gastric cancer	Stabilize HK2 mRNA	Promote Warburg effect	[89]
	Oncogene	circCMTM3	Hepatocellular carcinoma	Enhances m6A modification of circCMTM3	Inhibit ferroptosis	[39]
Therapeutic Resistance and Immune Evasion	Oncogene	-	Esophageal cancer	The lncRNA-EMS/miR-758-3p/WTAP axis	Promote cisplatin resistance	[31]
	Oncogene	PD-L1	Colorectal cancer	Stabilize PD-L1 mRNA	Promote immune evasion	[92]
Malignant Progression and Metastasis	Oncogene	TGF-β	Gastric cancer	Facilitate the expression and mRNA stability of TGF-β	Induce tumor epithelial-mesenchymal transition (EMT)	[32]
	Oncogene	MYC	Pancreatic cancer	Enhance MYC mRNA stability	Promote tumor cell proliferation and migration	[65]
	Oncogene	LKB1	Hepatocellular carcinoma	Increase the level of LKB1 mRNA	Inhibit tumor cell autophagy	[37]
Epigenetic Network Coordination	Oncogene	-	-	Form the m6A methyltransferase complex (MTC) with METTL3 and METTL14 that catalyzes m6A modification	-	[10]
	Oncogene	WTAPP1	Pancreatic cancer	Promote WTAPP1 translation and activating Wnt signaling	Promote PDAC progression	[25]
	Oncogene	VEGFA	Colorectal cancer	Upregulate VEGFA and activate MAPK pathway	Enhance angiogenesis	[45]

target of WTAP and overexpression of CCND1 can rescue the effects of WTAP knockdown in ESCC. Besides, WTAP promotes ESCC cell growth via the MAPK signaling pathway [35]. In addition, Zou *et al.* found that WTAP plays an oncogenic role in ESCC by promoting protein tyrosine phosphatase type IVA member 1 (PTP4A1) via m6A-dependent mechanisms. Mechanistically, WTAP activated PTP4A1 expression through the AKT-mTOR pathway, thus facilitating ESCC cell proliferation [36]. Furthermore, another study revealed the possible molecular mechanisms of WTAP in cell proliferation, migration and apoptosis. Knockdown of WTAP would reduce the expression of Ki67 and Snail, which were involved in cell proliferation and migration. Meanwhile, the expression of Bax and Caspase-3 was elevated, resulting in the increase of cell apoptosis [34].

Tumor microenvironment (TME), which contributes a lot to cancer drug resistance, has been drawing increasing attention. Hypoxia, a hallmark of TME characterized by oxygen deficiency, is prevalent in nearly all solid tumors and drives aggressive tumor behaviors [37]. Zhu *et al.* reported that hypoxia promotes the resistance of EC cells to cisplatin by regulating the lncRNA-EMS/miR-758-3p/WTAP axis. Mechanically, the expression of WTAP was induced in hypoxia. WTAP and miR-758-3p function as downstream targets of lncRNA-EMS, resulting in drug resistance against cisplatin in EC cells. Interestingly, overexpression of WTAP could half the apoptosis rate caused by cisplatin when miR-758-3p exists, indicating that WTAP was a downstream target of miR-758-3p and was essential for hypoxia-mediated resistance to cisplatin [38]. Gao *et al.* discovered that Caprin-1 was upregulated in EC tissues. Knockdown of Caprin-1 would inhibit the expression of METTL3 and WTAP which further suppress glycolysis, therefore inhibiting ESCA cell proliferation [39].

Gastric cancer (GC)

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [40].

Biological Role: It has been reported that WTAP shows a higher expression in GC, often indicating a poorer prognosis [23, 41, 42]. One study revealed that the expression of METTL3, WTAP and FTO proteins increases from normal tissue N to G1 stages, but declines from G1 to G3 stages [42]. These studies indicate that WTAP is an important biological marker for the prognosis and treatment of GC.

Mechanistic Insights: Overexpression of WTAP could facilitate the expression and mRNA stability of TGF-β, inducing GC cell EMT. Besides, WTAP plays an oncogenic role by promoting radiotherapy resistance and chemotherapy resistance to Cisplatin (DDP) and Cyclophosphamide (CTX) [43]. Furthermore, WTAP mediates m6A modification of circ0049271 which increases the expression of m6A reader IGF2BP3. Functionally, circ0049271 is overexpressed in malignantly transformed cells TGES-1 induced by the chemical carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and activates the TGF-β/SMAD pathway to promote GC cell proliferation, migration and invasion as well as EMT [44].

Epstein-Barr virus-associated gastric cancer (EBVaGC) is one of the GC subtypes and is related to EBV infection [45]. Previous research showed that in EBVaGC cell lines, WTAP expression was significantly more downregulated than that in Epstein-Barr virus-negative gastric cancer (EBVnGC) cell lines. Mechanically, EBV-encoded small RNA1 (EBER1) could inhibit WTAP expression via the NF-κB pathway. WTAP could promote GC cell proliferation but attenuate cell migration [46].

Pancreatic cancer (PC)

Pancreatic cancer is the seventh leading cause of cancer-related death worldwide and Pancreatic ductal adenocarcinomas (PDAC) accounts for 90 percent of pancreatic cancer. Pancreatic cancer is one of the most malignant cancers and the 5-year survival rate of patients with advanced-stage PDAC is only 11% [47].

Biological Role: Previous studies showed WTAP overexpression was closely related to CD8+ cell infiltration in PDAC cells and dendritic cells. However, there was no evidence indicating high expression of WTAP was associated with tumor mutation burden (TMB). Furthermore, WTAP expression was found to be closely associated with immune checkpoint regulation, highlighting its potential as a target for immunotherapy [48].

Mechanistic Insights: As a key m6A writer, WTAP mediates m6A modifications on downstream genes, thereby regulating their biological functions and influencing tumor progression. Glycogen-branching enzyme (GBE), encoded by the GBE1 gene, is an integral part of the glycogen biosynthesis pathway through compositing alpha-1,6-glucosidic branches from alpha-1,4-linked glucose chains [49]. A recent study found that WTAP and IGF2BP3 could stabilize GBE1 by regulating its m6A modification, thereby promoting the proliferation and stemness of PC cells [50]. Focal adhesion kinase (Fak) is a cytoplasmic protein tyrosine kinase which is upregulated in several solid cancers. Instead of adding m6A modifications, WTAP directly binds to Fak mRNA to enhance its stability, resulting in activating the Fak-PI3K-AKT and Fak-Src-GRB2-Erk1/2 signaling pathways. This ultimately results in enhancing PC cell migration and invasion [51]. Cao *et al.* reported that WTAP could increase m6A modification of MYC, which was recognized by m6A reader IGF2BP1 to enhance MYC mRNA stability. Gemcitabine could inhibit the WTAP/MYC axis to prevent PC cell proliferation and migration [52].

Gallbladder cancer (GBC)

Gallbladder is the most common of the biliary tract and there are over 110,000 new cases of GBC globally in 2020 [53].

Mechanistic Insights: Deoxycholic acids (DCA) are one of the most common bile acids which are stored in the gallbladder. A recent study identified DCA as a tumor suppressor whose downregulation indicated poorer prognosis of GBC patients. The m6A writer complex including WTAP modulates miR-92b-3p to regulate GBC cell proliferation. Mechanically, DCA promotes the disassociation of the m6A writer complex, which consequently inhibits the m6A modification of miR-92b-3p and attenuates its expression. Besides, in the process, the protein level of phosphatase and tensin homolog (PTEN), a critical tumor suppressor, which is the target of miR-92b-3p, was elevated, resulting in the activation of the PI3K/AKT signaling pathway [54].

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a malignant epithelial cancer that arises from the biliary tree and/or within the hepatic parenchyma and is divided into fluke-related and non-fluke-related CCA [55]. Recent studies had shown that WTAP was overexpressed in cholangiocarcinoma which facilitated cell migration and invasion. Besides, WTAP overexpression was closely associated with metastasis-related genes containing MMP7, MMP28, Cathepsin H, Muc1, S100b4 and GAS6, providing a potential therapeutic target for cholangiocarcinoma [56].

Liver cancer

Liver cancer is the third leading cause of cancer-related death with an estimated 865,000 new cases and 757,948 deaths in 2022. Primary liver cancer is mainly composed of Hepatocellular carcinoma (HCC), which accounts for 75-85% of the cases, and intrahepatic cholangiocarcinoma that constitutes 15% of newly diagnosed cases [57].

Biological Role: Previous studies have reported that WTAP was overexpressed in HCC [58-62], indicating a poor prognosis. Knockdown of WTAP could enhance HCC cell autophagy and attenuate cell proliferation [63].

To elucidate the discrepancies in WTAP expression patterns in HCC, we conducted a comprehensive analysis of studies reporting contradictory findings. Our investigation revealed that studies demonstrating WTAP overexpression in HCC predominantly utilized publicly available databases (e.g., TCGA and GEO) in their analyses, with some incorporating HCC tissue samples for additional validation. For instance, Chen et al. reported elevated WTAP expression at both mRNA and protein levels, with their findings corroborated by database analyses and immunohistochemistry (IHC)/tissue microarray (TMA) techniques, respectively [61]. In contrast, Liu et al. reported contradictory results without database validation. Their study, based on qPCR analysis of HCC tissues, demonstrated significantly reduced WTAP mRNA levels in tumor tissues compared to normal controls [64]. However, this finding lacked protein-level verification. While the preponderance of evidence supports WTAP overexpression in HCC, it is noteworthy that no study has yet confirmed this observation at the mRNA level using qPCR methodology - a critical gap in the current literature.

Several methodological considerations may contribute to these divergent findings: (1) variations in experimental approaches, (2) heterogeneity in patient-derived HCC tissue samples obtained from different medical institutions, and (3) relatively small sample sizes (n<70) across studies, which may introduce random variability. Future investigations should prioritize: (1) systematic qPCR-based quantification of WTAP mRNA levels in paired normal and HCC tissues, and (2) inclusion of larger, well-characterized patient cohorts to enhance statistical power and generalizability of findings.

Therefore, future research should focus on validating these findings across diverse cohorts and exploring the molecular mechanisms underlying the regulation of WTAP and its functional consequences in HCC progression. Higher levels of WTAP were associated with the increased interaction among cell cycle, cytokines and their receptors and chemokine signaling pathways. Besides, the upregulation of WTAP indicates enhanced immune cell infiltration, while knockdown of WTAP attenuates HCC cell proliferation and aggressiveness [58]. Mechanically, WTAP modulates the binding of HUR to target RNA in an m6A-dependent way [60].

Mechanistic Insights: Ferroptosis is a regulated cell death mechanism driven by iron-dependent accumulation of lipid peroxides, ultimately leading to oxidative membrane damage and cellular death, which is distinct from apoptosis, necrosis, and autophagy, and is driven by the accumulation of reactive oxygen species (ROS) and the depletion of glutathione (GSH), leading to membrane damage and cell death. Research by Dixon *et al.* first identified ferroptosis as a unique cell death mechanism [65], while Sun *et al.* highlighted its relevance in cancer therapy [66]. Recent evidence has demonstrated that triggering ferroptosis effectively targets and eliminates HCC cells, particularly those exhibiting heightened metabolic activity and iron dependency.

In HCC cells, WTAP increases m6A modification of circCMTM3 to enhance its expression and consequently attenuated ferroptosis by recruiting IGF2BP1 to stabilize PARK7. Inhibiting circCMTM3 and WTAP could decrease xenograft tumor growth in mice [67]. Besides, WTAP can induce m6A methylation of nitric oxide-associated protein 1 (NOA1) and the downregulation of WTAP could enhance the expression of glutathione peroxidase 4 (GPX4). GSH/GSSG levels were obviously increased following WTAP knockdown. Therefore, WTAP potentially influences the m6A methylation process of NOA1, leading to mitochondrial dysfunction, while simultaneously activating the GPX4-axis to suppress lipid oxidation, which thereby contributes to the progression of HCC [64]. Sulfatide was discovered to suppress the formation of the METTL3/METTL14/WTAP m6A writer complex through paired amphipathic helix protein (SIN3B)-mediated acetylation of its core components. Consequently, the m6A modification of metal response element binding transcription factor 1 (MTF1) was reduced and the 3'-UTR was identified as the major region of m6A modification. Then, the inhibition of m6A in MTF1 enhanced its mRNA stability and extended its half-life, resulting in poor prognosis. To summarize, the acetylation triggered by sulfatide governed the METTL3-METTL14-WTAP complex, thereby modulating MTF1 m6A methylation and mRNA transcription, which is a crucial process for the proliferation and metastatic spread of HCC [68].

Programmed death-ligand 1 (PD-L1) is a key immune checkpoint molecule which is expressed on tumor cells and other immune cells. It interacts with programmed cell death protein 1 (PD-1) on CD8+ T cells, delivering an inhibitory signal that suppresses T cell activation and promotes immune tolerance [69]. Previous research has reported that WTAP could target PD-L1 to affect CD8+ T cells' antitumor activity and consequently modulate tumorigenesis [70]. Yu *et al.* reported that WTAP promoted immune evasion and aerobic glycolysis in HCC, simultaneously impairing the antitumor cytotoxicity of CD8+ T cells. In contrast, genetic knockdown of WTAP mechanistically resulted in profoundly attenuated oncogenic phenotypes. Mechanistically, WTAP binds to the m6A site within the 3'-UTR of PD-L1 mRNA, thereby enhancing its stability. These findings demonstrate that WTAP suppresses the antitumor activity of CD8+ T cells, exacerbating HCC immune evasion and aerobic glycolysis [62]. Additionally, the knockdown of WTAP would decrease the m6A level of liver Kinase B1 (LKB1) mRNA to enhance its stability. Then, as an upstream kinase of AMP-activated protein

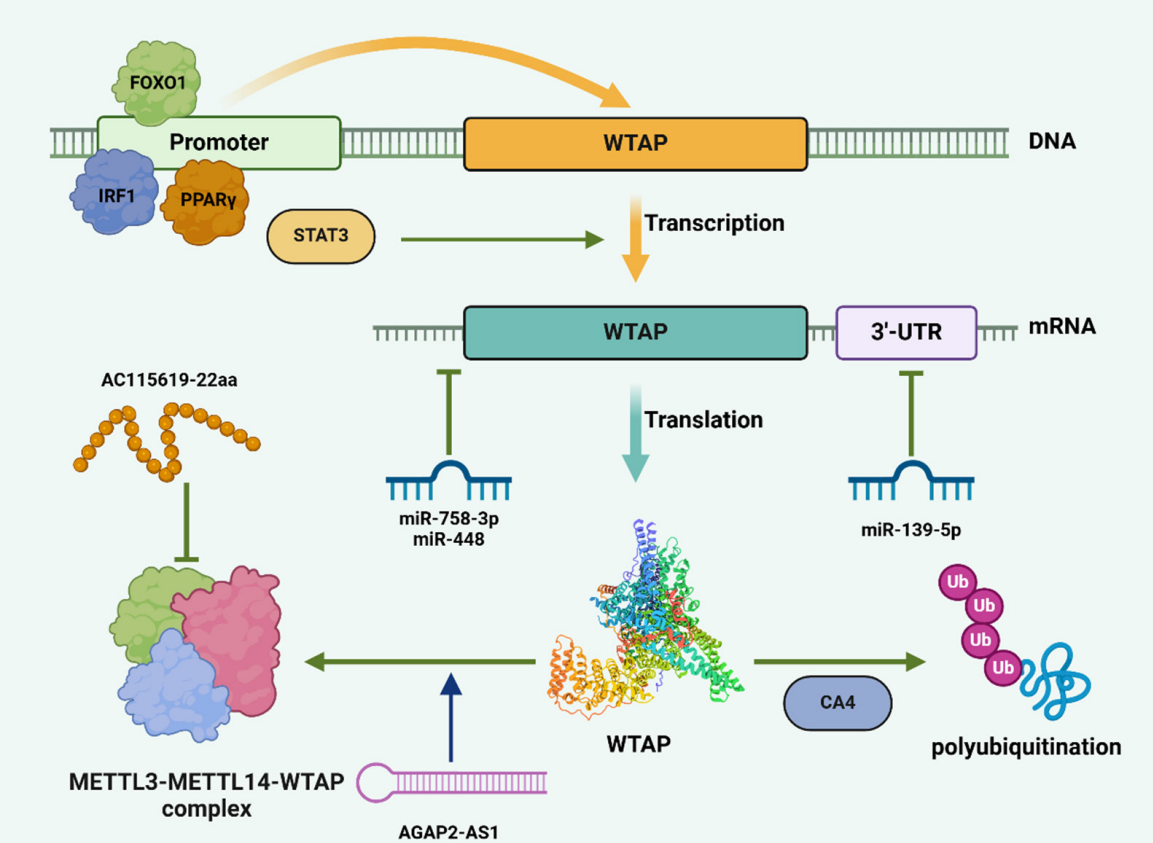

Figure 4. The potential upstream regulators of WTAP. FOXO1, IRF1 and PPARγ bind to the promoter region of WTAP to enhance its transcription, which maybe also upregulated by STAT3. microRNAs such as miR-139-5p could bind to the 3'-UTR of WTAP mRNA to inhibit its expression, while miR-758-3p and miR-448 target WTAP mRNA to restrain its expression as well. CA4 directly interacts with WTAP and triggers its polyubiquitination-mediated protein degradation. AGAP2-AS1 enhances the formation of the WTAP/METTL3/METTL14 complex to promote m6A modification. Conversely, AC115619-22aa binds to WTAP, disrupting the assembly of WTAP/METTL3/METTL14 complex and acts as a tumor suppressor. FOXO1, forkhead box protein O1; IRF1, interferon regulatory factor 1; PPARγ, peroxisome proliferator activated receptor γ; STAT3, signal transducer and activator of transcription 3; CA4, carbonic anhydrase IV.

kinase (AMPK), the increased LKB1 level would upregulate p-AMPK to promote cell autophagy, thus inhibiting proliferation [63].

Zhang *et al.* reported that under normoxic and hypoxic conditions, METTL3 and WTAP suppressed the expression of tumor suppressor proliferator-activated receptor-gamma coactivator-1α (PPARGC1A) expression through an m6A-YTHDF2-dependent mechanism by decreasing its stability. Meanwhile, silencing WTAP promoted the luciferase activity of PPARGC1A 3'-UTR-fused reporter plasmids. Conversely, hypoxia increased m6A modification of PPARGC1A and destabilized it. BAMBI acted as a downstream gene of PPARGC1A to affect HCC cell growth and metastasis. In conclusion, the PPARGC1A/BAMBI/ACSL4 axis exhibited responsiveness to hypoxia, with PPARGC1A mRNA being regulated via WTAP-associated m6A modification under hypoxic conditions [71]. The potential upstream regulators of WTAP are summarized in **Figure 4**.

In recent years, researchers have identified a cascade of upstream genes which regulate the expression of WTAP, thereby altering the m6A modification of downstream genes and ultimately impacting HCC tumorigenesis. WTAP, a crucial component of the methyltransferase complex, was transcriptionally upregulated by signal transducer and activator of transcription 3 (STAT3), leading to the nuclear localization of METTL3 and enhancing its methyltransferase activity [72]. Additionally, Zhang *et al.* identified AC115619 as an HCC suppressor that encodes

a micropeptide named AC115619-22aa. Mechanistically, AC115619-22aa could bind to WTAP, disrupting the assembly of the m6A methyltransferase complex and counteracting the tumor-promoting effects of WTAP in HCC cells. By inhibiting this complex, AC115619-22aa indirectly modulates m6A-regulated cancer-promoting and cancer-suppressing genes (such as SOCS2 and ATG14), thereby suppressing HCC progression [73].

Colorectal cancer (CRC)

Colorectal cancer is one of the most prevalent malignancies globally, ranking as the second leading cause of cancer-related mortality, with over 900,000 deaths in 2020 [74]. The high mortality rate in CRC patients is primarily attributed to frequent metastasis and recurrence, which significantly complicate treatment outcomes [75]. Epigenetic alterations can influence gene expression patterns, tumor microenvironment interactions, and therapeutic resistance, providing potential targets for novel treatment strategies [76].

Biological Role: Previous studies have reported that WTAP is significantly overexpressed in CRC cells and tissues [77-81], and high expression of WTAP is negatively correlated with tumor differentiation, indicating a poorer prognosis [82, 83]. Moreover, WTAP enhances the migratory, proliferative, and invasive capabilities of CRC cells while simultaneously suppressing apoptosis [78, 79, 82]. However, existing studies have found no significant association between WTAP expression levels and the prognosis of CRC patients [77].

Mechanistic Insights: WTAP facilitates the m6A modification of NLR Family Pyrin Domain Containing 3 (NLRP3), leading to the suppression of NLRP3 expression and the inhibition of the NLRP3/Caspase-1/GSDMD axis activation, as well as pyroptosis, which ultimately promoted the malignant progression of CRC [78]. Another study reported that WTAP dampened oxaliplatin chemosensitivity in HCT116 and DLD1 cells. Mechanistically, oxaliplatin treatment increases WTAP expression, thereby suppressing PANoptosis (pyroptosis, apoptosis, and necroptosis) activation.

This is achieved through the m6A-dependent maintenance of nuclear factor erythroid-2-related factor 2 (NRF2), a key antioxidant regulator. In clinical contexts, elevated WTAP expression in CRC patients is correlated with poorer prognosis and reduced responsiveness to conventional chemotherapy [84]. Mechanistically, WTAP orchestrates epigenetic silencing of the tumor suppressor FLNA through m6A deposition at its 3'-UTR, inducing transcript destabilization via YTHDF2 recognition, which subsequently impairs autophagic flux in colorectal carcinogenesis [79]. Besides, WTAP acts as an upstream regulator of SRY-box transcription factor 1 (SOX1), modulating its expression through m6A modification, which leads to the post-transcriptional suppression of SOX1. This process is facilitated by YTHDF2, which promotes mRNA degradation. SOX1, in turn, inhibits the progression of CRC.

Therefore, WTAP controls the proliferation, migration, and invasion of CRC cells by regulating SOX1 in an m6A-YTHDF2-dependent manner [82]. WTAP interacts with m6A binding sites within Pyruvate Dehydrogenase Kinase 4 (PDK4). Silencing PDK4 enhances the viability, proliferation, migration, and invasion of CRC cells, suppresses PDK4 expression, and promoted the growth of xenografts *in vivo*.

In contrast, WTAP depletion produced the opposite effects and counteracted the consequences of PDK4 silencing [80]. Ye *et al.* reported that the overexpression of WTAP intensified cellular proliferation, migration, invasion, and the formation of new blood vessels. Mechanically, WTAP promoted vascular endothelial growth factor A (VEGFA) expression by regulating its m6A modification, which was recognized by m6A reader YTHDC1. And the proliferation of CRC cells is driven by the WTAP/YTHDC1/VEGFA axis through the activation of the MAPK signaling pathway [81].

Furthermore, the ANKLE1 rs8100241-A variant was associated with a lower risk of CRC through its role in diminishing genomic instability [85]. Similarly, the single-nucleotide polymorphism rs11245997, located in the 3'-UTR of BET1L, was found to be significantly linked to an increased risk of colorectal cancer. The A allele of rs11245997 enhanced BET1L expression by interfering with the binding of miR-140-3p. Additionally, this allele reduced m6A modification of BET1L, leading to its upregulation through mechanisms involving the m6A methyl-

transferases METTL14 and WTAP, as well as the m6A demethylase ALKBH5, while elevated BET1L expression was correlated with more advanced tumor stages and poorer patient outcomes. On the other hand, increased BET1L expression stimulates the growth of colorectal cancer cells [86].

As for the upstream regulators of WTAP, TTC22 was identified to be co-expressed with WTAP and FTO across multiple tissues. The direct interaction between TTC22 and the RPL4 facilitated the binding of WTAP mRNA to RPL4, thereby enhancing the stability and translational efficiency of WTAP mRNA, which ultimately led to an elevation in WTAP protein levels. Additionally, WTAP mRNA itself was subject to m6A modification, with YTHDF1 identified as a critical m6A-binding protein that interacted with WTAP mRNA. TTC22 initiated a positive feedback loop that amplified both WTAP expression and the m6A modification of WTAP mRNA, resulting in an overall increase in m6A levels across total RNA. TTC22 enhanced the expression of WTAP and SNAI1, thereby playing a role in promoting colon cancer metastasis [24].

Moreover, NT5DC3 was identified, with hexokinase domain component 1 (HKDC1) potentially acting as a downstream effector of NT5DC3. Mechanistically, the expression of NT5DC3 was transcriptionally regulated by lactoferrin (LF)-dependent remodeling of cellular DNA 5mC and RNA m6A profiles. WTAP played a crucial role in modulating NT5DC3 m6A modification, thereby influencing the expression of its downstream target, HKDC1. Additionally, combined treatment with lactoferrin and NT5DC3 protein inhibited colon tumor growth by modifying abnormal epigenetic markers. Notably, analysis of blood samples revealed that NT5DC3 protein expression is essential for distinguishing individuals with Type 2 diabetes (T2D) or T2D-induced colon cancer from healthy individuals [87].

Targeting WTAP for potential clinical prospects: mechanisms and therapeutic implications

The m6A modifications mediated by WTAP play a crucial role in regulating RNA stability, translation, and degradation. By modulating m6A levels, WTAP influences the expression of key oncogenes and tumor suppressors. Mechanistically, WTAP-mediated m6A modifications can stabilize oncogenic mRNAs, such as MYC in pancreatic cancer [52], promoting tumor cell proliferation and survival. Therefore, inhibiting WTAP could destabilize these oncogenic mRNAs, leading to reduced tumor growth and enhanced sensitivity to chemotherapy.

In addition, WTAP has been shown to regulate tumor metabolism, particularly the Warburg effect, which is characterized by increased glycolysis even in the presence of oxygen. This metabolic shift is considered a hallmark of cancer and supports rapid tumor growth. In gastric cancer, WTAP stabilizes HK2 mRNA, a key enzyme in glycolysis, promoting the Warburg effect and stimulating tumor cell proliferation [88]. Similarly, in colorectal cancer, WTAP regulates forkhead box protein 3 (FOXP3) and SMARCE1, promoting glycolysis and tumor growth [89]. Targeting WTAP could suppress tumor metabolism, potentially enhance the efficacy of metabolic inhibitors and reducing tumor growth.

Moreover, WTAP plays a significant role in mediating drug resistance in various cancers, often through m6A-dependent mechanisms that stabilize mRNAs involved in resistance pathways. In esophageal cancer, WTAP is involved in hypoxia-induced cisplatin resistance through the lncRNA-EMS/miR-758-3p/WTAP axis [38]. And decreasing WTAP expression could reverse drug resistance, making tumors more susceptible to chemotherapy and immunotherapy.

Malignant tumors employ sophisticated immune evasion mechanisms through which neoplastic cells circumvent host immunosurveillance, enabling their proliferation and metastatic dissemination even in the presence of persistent anti-tumor immunity. According to previous studies, WTAP has been implicated in immune evasion by regulating the expression of immune checkpoint molecules, such as PD-L1, which suppresses T cell activity and promotes tumor immune escape. In HCC, WTAP enhances the stability of PD-L1 mRNA through m6A modification, suppressing the antitumor activity of CD8+ T cells and promoting immune evasion [62]. Targeting WTAP could enhance the efficacy of immune checkpoint inhibitors by reducing PD-L1 expression and restoring T cell-mediated antitumor immunity.

Besides, several studies have reported that WTAP could promote EMT, a process by which epithelial cells acquire mesenchymal traits, facilitating tumor cell migration, invasion, and metastasis. Restraining WTAP could suppress EMT, reducing tumor metastasis and improving patient outcomes.

WTAP has been shown to regulate ferroptosis in hepatocellular carcinoma. WTAP enhances the m6A modification of circCMTM3, which recruits IGF2BP1 to stabilize PARK7, thereby attenuating ferroptosis in HCC cells [67]. Additionally, WTAP regulates ATG5 expression through m6A modification, contributing to ferroptosis resistance [90]. Thus, targeting WTAP could induce ferroptosis in cancer cells, offering a novel therapeutic strategy for HCC and other cancers. Moreover, the tumor microenvironment, particularly hypoxia, plays a critical role in tumor progression and drug resistance. WTAP has been shown to mediate hypoxia-induced resistance in various cancers. In esophageal cancer, hypoxia promotes cisplatin resistance through the lncRNA-EMS/miR-758-3p/WTAP axis [38]. In colorectal cancer, hypoxia enhances WTAP-mediated stabilization of PD-L1 mRNA, contributing to immune evasion [91]. Therapeutic strategies aimed at WTAP could potentially overcome hypoxia-driven resistance mechanisms, thereby boosting the efficacy of chemotherapy and immunotherapy in hypoxic tumor environments.

However, few therapies or drugs targeting WTAP have been developed for clinical use in cancer treatment. These findings underscore the need for systematic investigation of WTAP's therapeutic implications, warranting functional validation in diverse clinically relevant models spanning patient-derived xenografts, organotypic cultures, and longitudinal clinical cohorts to delineate context-dependent mechanisms and translational applications, including but not limited to immunotherapy development, chemotherapy optimization, applications of WTAP inhibitors, and advanced siRNA delivery systems utilizing nanotechnology.

Despite considerable potential in the clinical applications of WTAP, significant limitations persist due to its complex biological roles and technical challenges. A primary concern is its tissue-specific and context-dependent functionality; while WTAP predominantly acts as an oncogene in most gastrointestinal cancers, it paradoxically exhibits tumor-suppressive effects in subsets of hepatocellular carcinoma by promoting mitochondrial dysfunction and ferroptosis. This functional duality complicates the development of universal targeting strategies. Molecularly, WTAP operates within the METTL3-METTL14-WTAP methyltransferase complex, creating functional redundancy where its inhibition may be compensated by other m6A regulators. The absence of selective, clinically viable inhibitors, current approaches rely on genetic tools like siRNA, which are unsuitable for systemic delivery further impedes translational progress. Additionally, most studies on WTAP focus on its molecular mechanisms as an m6A writer, with few organizing clinical trials to validate these findings. Consequently, drugs targeting WTAP remain need further investigation for clinical application.

Conclusion

We focus on the structure, biological effects and mechanisms of WTAP, as well as its value in the diagnosis and therapy of digestive system cancers. WTAP is a critical component of MTC, playing a pivotal role in RNA methylation and influencing various biological processes in cancer. As a key m6A writer, WTAP, along with METTL3 and METTL14, catalyzes the addition of m6A modifications to RNA, regulating RNA stability, translation, and degradation [10, 20, 21]. Through these mechanisms, WTAP modulates the expression of oncogenes and tumor suppressors, impacting cancer cell proliferation, migration, invasion, and apoptosis.

In digestive system malignancies, WTAP has usually been shown to be overexpressed and associated with poor prognosis, advanced tumor stages, and increased metastases. It promotes tumorigenesis by stabilizing oncogenic mRNAs, enhancing the Warburg effect, and facilitating EMT [43, 88, 92]. Additionally, WTAP contributes to drug resistance by stabilizing mRNAs involved in resistance pathways, such as PD-L1, which promotes immune evasion by suppressing T cell activity. WTAP also plays a role in regulating ferroptosis and influences the tumor microenvironment, particularly under hypoxic conditions, further contributing to cancer progression and therapy resistance [52, 88, 91].

Furthermore, targeting WTAP can induce ferroptosis in cancer cells, offering a novel therapeutic strategy for cancers like HCC [67, 90]. Mechanistic integration of WTAP with oncogenic signaling cascades, notably MAPK proliferative signaling, AKT pro-survival cascades, and Wnt-driven epithelial plasticity programs, through the epigenetic modulation of m6A deposition functionally positions this RNA-binding protein as a pivotal coordinator of tumorigenic reprogramming and therapeutic vulnerability [25, 35, 38].

Although most studies describe WTAP as an oncogene, which is highly expressed in tumor tissues and is related to poor prognosis, there are a few studies reporting that the downregulation of WTAP in HCC induced low mitochondrial membrane potential in Huh-7 and SNU-449 cells [64].

Emerging evidence indicates that WTAP promotes tumorigenesis by regulating m6A modifications of downstream genes. However, some studies noted that WTAP could induce mitochondrial damage and ferroptosis by modulating the m6A modification of NOA1 and consequently suppress tumor progression [64]. In addition, although multiple studies have pointed out that WTAP could be a therapeutic target and complex mechanisms have been discovered, there is still no feasible treatment targeting WTAP that was employed in clinical cases.

In the future, more research should focus on validating these findings across diverse cohorts and exploring the molecular mechanisms underlying WTAP regulation in tumor progression. Targeting WTAP may provide new insights into cancer treatment, offering potential strategies to overcome treatment resistance and achieve better outcomes.

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Disclosure of conflict of interest

None.

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