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Complicated role of ALKBH5 in gastrointestinal cancer: an updated review

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Abstract

Gastrointestinal cancer is the most common malignancy in humans, often accompanied by poor prognosis. N6-methyladenosine (m6A) modification is widely present in eukaryotic cells as the most abundant RNA modification. It plays a crucial role in RNA splicing and processing, nuclear export, translation, and stability. Human AlkB homolog 5 (ALKBH5) is a type of RNA demethylase exhibiting abnormal expression in various gastrointestinal cancers.It is closely related to the tumorigenesis, proliferation, migration, and other biological functions of gastrointestinal cancer. However, recent studies indicated that the role and mechanism of ALKBH5 in gastrointestinal cancer are complicated and even controversial. Thus, this review summarizes recent advances in elucidating the role of ALKBH5 as a tumor suppressor or promoter in gastrointestinal cancer. It examines the biological functions of ALKBH5 and its potential as a therapeutic target, providing new perspectives and insights for gastrointestinal cancer research.

Keywords Gastrointestinal cancer, ALKBH5, m6A, Epigenetics

Background

Gastrointestinal cancer is among the most common and deadly tumors worldwide, accounting for approximately one-fourth of the global cancer incidence and a mortality rate as high as one-third [1]. Although current conventional treatments, such as surgical resection, chemotherapy, and radiotherapy, are used for treating gastrointestinal cancer, the risks of cancer recurrence and drug resistance remain high. Precision targeting of tumors holds great promise in cancer therapy, leading to more in-depth research and analysis of cancer.

Epigenetic modifications are alterations independent of the DNA sequence [2], primarily regulating gene expression at the transcriptional level. Discoveries have been made in various aspects, including DNA and RNA methylation [3, 4], histone modifications [5], transcriptional control [6], chromatin remodeling [7], non-coding RNA [8], and cancer immunotherapy [9]. Recent research indicated that cancer cells are often regulated by relevant epigenetic proteins, which are essential for maintaining normal cell growth, inducing differentiation, and initiating, sustaining, and propagating disease and abnormal cell states [10]. There is growing evidence indicating that epigenetic modifications, especially RNA modifications play a crucial role in tumorigenesis [11, 12].

With the development of high-throughput sequencing technologies, over 170 RNA modifications have been

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identified, and m6A modification is one of the most prevalent types [13]. Transcriptome sequencing reveals that m6A binding sites are found within the RRACH sequence (R = A/G, H = A/C/U), predominantly enriched in the 3' untranslated regions (UTRs) near the termination codon of mRNA exons [14, 15]. M6A modification participates in various RNA metabolism processes, including splicing, nuclear export, translation, decay, processing, and RNA-protein interactions. Additionally, it plays a crucial role in embryonic stem cell differentiation, meiosis, tissue development, circadian rhythm, and tumor occurrence[16–20]. M6A modification is a dynamic and reversible process, which is primarily led by methyltransferases (Writers), demethylases (Erasers), and identified and promoted by some specific RNA-binding proteins (Readers)[21](Fig. 1).

Up to now, methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), methyltransferase-like 16 (METTL16), Wilms tumor 1 associated protein (WTAP), zinc finger CCCH-type containing 13 (ZC3H13) proteins, RNA-binding motif protein 15 (RBM15), Vir-like m6 A methyltransferase-associated (VIRMA/KIAA1429), Cbl proto-oncogene like1 (CBLL1/Hakai), and Fl(2)d-associated complex component (Flacc) were regarded as Writers, and they can interact with each other to form a stable methyltransferase complex (MTC), or plays a supporting role in catalyzing the heterodimeric methyltransferase activity [22–31](Fig. 1). Erasers, including Fat mass and obesity-associated

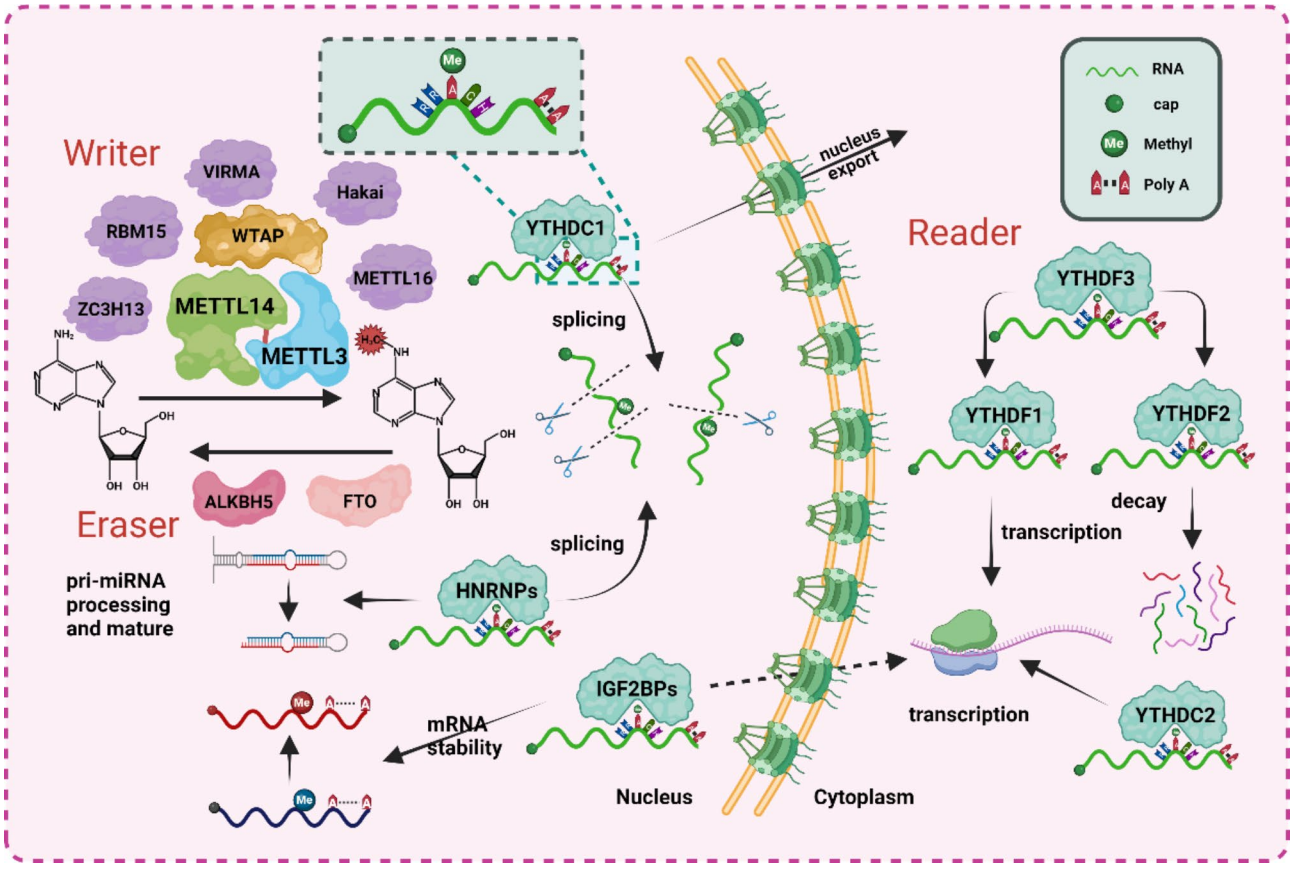

Fig. 1 Molecular mechanism of m6A modification. M6A is mediated by writers, erasers and readers, the details are as follows. METTL14 binds to METTL3 and forms a stable MTC. WTAP recruits MTC and localizes it in the nuclear speckle, performing a function that aids in catalyzing the activity of methyltransferases. ZC3H13, RBM15, and VIRMA act on the MTC to regulate the occurrence of m6A methylation. Hakai serves as a core component of the m6A writer and interacts with other writers. METTL16, which is a conserved U6 snRNA methyltransferase, controls the homeostasis of S-adenosylmethionine (SAM) by post-transcriptionally regulating the expression of SAM synthase genes. FTO and ALKBH5 belong to the family of ketoglutarate-dependent dioxygenases, mediating the reverse process of m6A methylation under the action of Fe(II) and α-ketoglutarate. YTHDF2 is the first discovered m6A reader protein, regulating the degradation of mRNA. YTHDF1 can promote the translation of m6A-modified mRNAs by binding to m6A sites and regulating translation factors. YTHDF3 can act on YTHDF1 to enhance the translation of mRNAs, and it can also act on YTHDF2 to regulate the degradation of mRNAs. YTHDC1 regulates the splicing function of mRNAs by recruiting splicing factors, and it also mediates m6A-dependent nuclear export. YTHDC2, as an RNA helicase, can enhance the translation efficiency of mRNAs while reducing their RNA abundance. IGF2BPs recognize the GG(m6A)C sequence and promote the stability, translation, and storage of targeted mRNAs. HNRNPs regulate the processing, and maturation of miRNAs and the abundance and splicing of mRNAs in an m6A-dependent manner. (figure was created with Biorender.com)

protein (FTO) and ALKBH5, are central to the removal of m6A modifications [32, 33]. They are part of the alpha-ketoglutarate-dependent dioxygenase family, mediating the reverse process of m6A methylation under the action of Fe(II) and α-ketoglutarate[34]. FTO is involved in the regulation of the cell cycle, cell differentiation, splicing, cancer development, immunotherapy, and various other biological functions [35–38]. Importantly, ALKBH5, as another member of the α-ketoglutarate-dependent dioxygenase family, was found that knocking out ALKBH5 not only increases the m6A levels of RNA inside cells but also enhances the export of these RNAs from the nucleus to the cytoplasm [33]. Readers mainly include the YT521-B homology (YTH) domain family, IGF2 mRNA binding protein (IGF2BPs), and heterogeneous nuclear ribonucleoproteins (HNRNPs)[39–47]. And they mainly play a role in post-transcriptional regulation by identifying and binding to m6A-targeted genes, regulating downstream functions (Fig. 1).

Among these regulators, ALKBH5, which was first discovered in 2013 as a demethylase for m6A, is becoming a hub in the research of epigenetic regulation of the development of cancer cells. The complicated biological functions of ALKBH5 have been widely found to be involved in various gastrointestinal cancers, including gastric cancer (GC), colorectal cancer (CRC), liver cancer (LC), pancreatic cancer (PC), and esophageal squamous cell carcinoma (ESCC). This review will focus on the role of ALKBH5 in gastrointestinal cancer and discuss directions for future research and potential clinical application of ALKBH5 for gastrointestinal cancer.

The structure and role of ALKBH5

ALKBH5 is a member of the AlkB family, a 2-oxoglutarate and ferrous acid-dependent nucleic acid oxygenase. It is located on human chromosome 17p11.2. Human ALKBH5 has a full length of 394 amino acids and its catalytic core contains features of a double-stranded β-helix fold (DSBH). Aik W et al. suggested that the DSBH fold of ALKBH5 is composed of eight reverse parallel β-strands, with the major β-sheet consisting of β6, β8, β11, and β13, and the minor β-sheet being formed by β7, β9, β10, and β12 [48]. However, Feng C et al. suggested that the DSBH fold of ALKBH5 does not have the typical eight reverse parallel β-strands, where β4, β5, β8, and β9 form the major sheet while β6, β7, and a short α-helix (α7) plus a long loop (C1) form the minor sheet [49]. The unique structural feature of ALKBH5 that plays an important role in substrate recognition and catalysis is the nucleotide recognition caps called "Flip1" and "Flip2" outside the DSBH fold. In addition, a disulfide bond formed between Cys-230 and Cys-267 has been identified in ALKBH5, and this structure is believed to underlie the selectivity of ALKBH5 for single-stranded substrates [48, 49].

Normally, ALKBH5 is highly expressed in the testis, and it has been found that increased m6A expression in ALKBH5-deficient male mice affects apoptosis in mid-meiotic spermatocytes, leading to impaired fertility [33, 50]. In addition to the fact that ALKBH5 can affect the spermatogenesis process, Pollard PJ et al. discovered that ALKBH5 is directly regulated by hypoxia-inducible factor 1α (HIF-1α), an oxygenase dependensst on 2-oxoglutarate (2OG) that is induced under hypoxic conditions. [51]. It has also shown that ALKBH5 can affect osteogenesis in ligamentum flavum cells through the protein kinase B (AKT) signaling pathway [52], as well as the osteogenic process through the NF-κB (nuclear factor-κB) signaling pathway [53].

The role of ALKBH5 in gastrointestinal cancer

Increasing evidence suggests that the m6A demethylase ALKBH5 is aberrantly expressed in various gastrointestinal cancers, closely associated with tumorigenesis, tumor proliferation, migration, invasion, and more (Table 1), making it a potential novel target for cancer treatment (Fig. 2). In the following section, we discuss the expression of ALKBH5 in gastrointestinal cancer and the mechanisms involved.

Colorectal cancer

CRC is the third deadliest cancer in the world, ranking consistently among the top three in both incidence and mortality rates among all cancer types. It accounts for approximately 10% of all cancer-related deaths each year [54]. Despite increasing research and treatment efforts dedicated to colorectal cancer each year, many molecular mechanisms remain unclear. There is growing evidence that m6A modification plays a crucial role in the molecular regulation of CRC (Fig. 3).

Bioinformatics results revealed a decreased expression of ALKBH5 in CRC. Its expression is strongly correlated with survival prognosis, staging, distant metastasis, and the American Joint Committee on Cancer (AJCC) stage, establishing it as one of the independent prognostic indicators for CRC. Immune checkpoint inhibitor therapy, as one of the mature approaches in current cancer treatment, is often less effective due to the low immunogenicity of cold tumors. ALKBH5, in collaboration with YTHDF1, can impact the immune environment, promoting the transformation of colon adenocarcinoma (COAD) patients from the cold tumor type to the hot tumor type [55, 56], greatly enhancing the effectiveness of immunotherapy. ALKBH5 can bind to the Wnt pathway inhibitor AXIN2, inducing its degradation, thereby activating Wnt/β-catenin and its associated protein Dickkopf-related protein 1 (DKK1). This process induces

Table 1 The function of ALKBH5 as an m6A methyltransferase in gastrointestinal cancer

Cancer type	Expression	Role	Targets	Biological function	Reader	Ref
Colorectal cancer	↓	Suppressor		Inhibits invasion, migration		[55]
	↓	Suppressor	PD1; CTLA4	Transform cold tumors into hot tumors	YTHDF1	[56]
	↓	Suppressor	NF-κB-CCL5	Inhibits proliferation, migration, invasion; Promotes CD8 + T cell infiltration		[58]
	↓	Suppressor	PHF20	Inhibits proliferation, migration, invasion	IGF2BP3	[59]
	↓	Suppressor	JMJD8; PKM2	Promotes glycolysis	IGF2BPs	[60]
	↓	Suppressor	FOXO3/miR-21/ SPRY2	Inhibits proliferation and migration		[63]
		/	circAFF2/Cullin-NEDD8	Enhances the radiosensitivity of CRC cells	YTHDF2	[64]
	↓	Suppressor	SLC7A11	Promotes ferroptosis of CRC cells		[65]
	↑	Oncogene	AXIN2; Wnt; DKK1	Promotes immune suppression	IGF2BP1	[57]
	↑	Oncogene	RAB5A	Promotes proliferation, migration, invasion	YTHDF2	[61]
	↑	Oncogene	lncRNA NEAT1	Promotes proliferation and migration; Promotes cell apoptosis		[62]
Hepatocellular carcinoma	↑	Oncogene	MAP3K8	Promotes proliferation, and migration; Promotes macrophage recruitment	YTHDF2	[67]
	↓	Oncogene		Promotes migration		[70]
		Oncogene	LINC02551	Promotes growth and migration of HCC cells	IGF2BP1	[71]
	↓	Suppressor	PAQR4	Inhibits proliferation, migration, invasion	IGF2BP1	[72]
	↓	Suppressor	LYPD1	Inhibits proliferation, invasion	IGF2BP1	[73]
			TIRAP/NF-Kb; CCL5	Promotes HSC activation; Promotes monocyte recruitment and M2 polarisation; Decreases radiosensitivity of hepatocellular carcinoma	YTHDF2	[74]
Intrahepatic cholangiocarcinoma			PD-L1	Accelerates the degradation of PD-L1 mRNA; Decreasing the infiltration of myeloid-derived suppressor-like cells	YTHDF2	[68]
Liver cancer stem cells	↑	Oncogene	SOX4;SHH	Promotes proliferation, migration and invasion		[69]
Pancreatic cancer	↓	Suppressor	PER1	Inhibits proliferation, migration, invasion	YTHDF2	[76]
	↓	Suppressor	KCNK15-AS1	Inhibits migration and invasion		[77]
	↓	Suppressor	KCNK15-AS1; PTEN/AKT signaling	Inhibits proliferation, migration, and epithelial-mesenchymal transition (EMT); Promotes cell apoptosis		[78]
Pancreatic ductal adenocarcinoma	↓	Suppressor	FBXL5	Inhibits migration, and invasion; Reduces iron metabolism and EMT	YTHDF1	[79]
	↓	Oncogene	WIF-1; Wnt signaling	Promotes proliferation, migration, invasion		[80]
		Oncogene	DDIT4-AS1; mTOR pathway	Maintains pancreatic cancer stemness; Suppresses chemosensitivity		[81]
Gastric cancer	↑	Oncogene	JAK1	Promotes proliferation and migration	YTHDF2	[83]
		Oncogene	Nanog	Promotes proliferation and tumorigenicity of GC cells		[84]
		Oncogene	lncRNA NEAT1	Promotes invasion and metastasis		[85]
	↓	Suppressor	PKMYT1	Inhibits invasion and migration	IGF2BP3	[86]
Esophageal squamous cell carcinoma	↓	Suppressor		Inhibits proliferation, migration and invasion		[88]

↓: downregulated; ↑: Upregulated;

DKK1 to recruit inhibitory cells derived from the bone marrow, driving immune suppression in CRC [57]. Overexpression of ALKBH5 suppresses CRC cell proliferation, migration, and invasion. It alleviates the malignant progression of CRC by promoting CD8(+) T cell infiltration in the tumor microenvironment through the NF-κB (nuclear factor-κB)-CCL5(C-C motif chemokine ligand 5) axis [58]. Furthermore, related studies suggest that ALKBH5 is downregulated in CRC and is associated with poor prognosis in CRC patients. ALKBH5 can suppress the occurrence and development of CRC by removing the methylation modification of its downstream target gene plant homeodomain finger protein 20 (PHF20), thereby reducing the mRNA stability of PHF20 [59]. Wu and

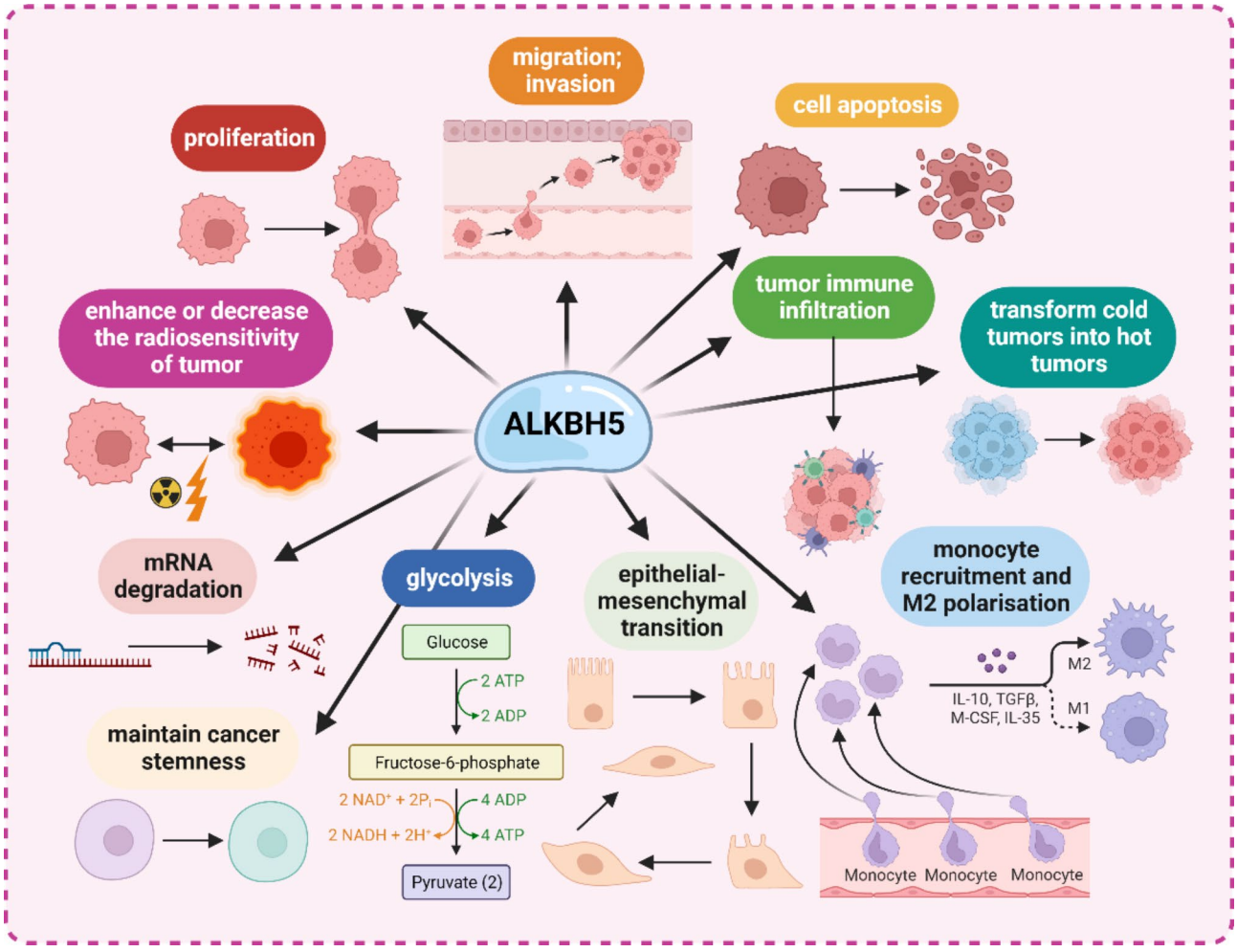

Fig. 2 Biological functions of ALKBH5 in gastrointestinal cancer. ALKBH5 regulates tumor cell proliferation, migration, and invasion. ALKBH5 also controls monocyte recruitment and M2 polarization, as well as cellular autophagy. ALKBH5 also plays a role in tumor immune infiltration, hot/cold tumor transition, and the enhancement or attenuation of tumor radiosensitivity. It can also regulate epithelial-mesenchymal transition, stemness maintenance, glycolysis, and RNA degradation. (figure was created with Biorender.com)

colleagues discovered that improving the identification and delivery system for CRC treatment can effectively alleviate the development of CRC. They confirmed the effectiveness of this approach in mitigating CRC development by synthesizing folate-modified exosome-liposome hybrid nanoparticles loaded with ALKBH5 mRNA and utilizing nano therapy to modulate the ALKBH5/JMXD8/PKM2 (Pyruvate kinase M2) axis and suppress glycolysis [60].

It is worth noted that experimental results from some scholars indicate that ALKBH5 can act as an oncogene, promoting the occurrence and development of CRC. That suggests that ALKBH5 may have a dual regulatory role in CRC. Shen et al. discovered that ALKBH5 can function as an upstream target of a Rab GTPase family protein (RAB5A), and through m6A-YTHDF2-dependent mechanisms, reduce the mRNA degradation efficiency of RAB5A, increasing the expression of RAB5A, thereby promoting the progression of CRC [61]. The regulation of CRC by ALKBH5 in non-coding RNA has also been reported. The ALKBH5-LncRNA NEAT1 (lncRNA nuclear paraspeckle assembly transcript 1) axis may serve as a potential therapeutic target for CRC. NEAT1 is upregulated in CRC and is associated with poor prognosis, and ALKBH5 promotes the progression of COAD by reducing the methylation of lncRNA NEAT1 [62]. ALKBH5 can decrease the m6A modification of Forkhead box O3 (FOXO3), and enhance the RNA stability of FOXO3. Thus, it targets miR-21 through FOXO3 and increases sprouty2 (SPRY2) expression, forming the FOXO3/miR-21/SPRY2 axis to regulate the progression of CRC [63]. Research indicates that CircRNA AFF2 is highly expressed in radiation-sensitive colorectal cancer patients, and those with high expression have a better prognosis. Its regulation is closely associated with the ALKBH5/YTHDF2 m6A-dependent pathway. CircAFF2

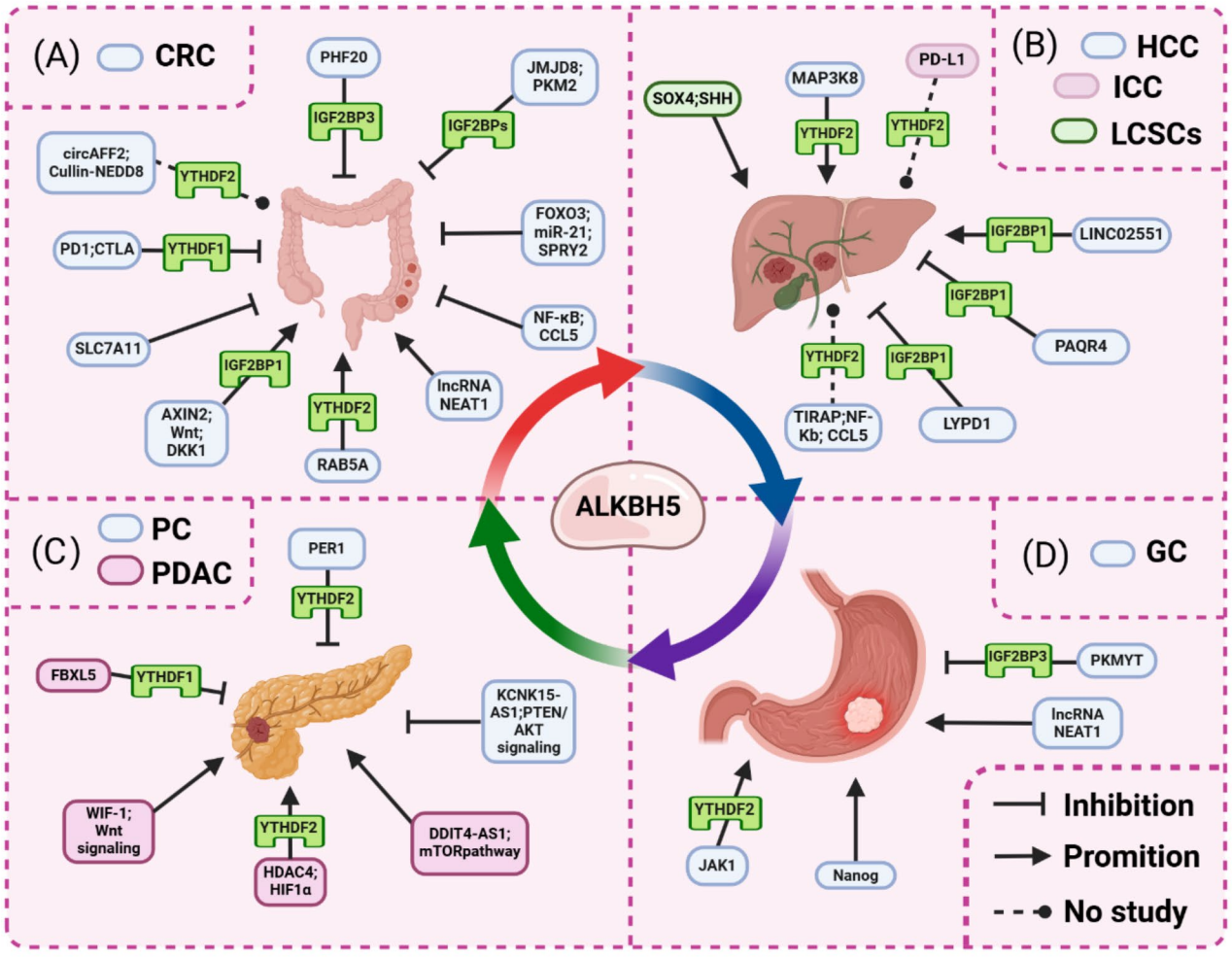

Fig. 3 ALKBH5 promotes or inhibits the progression of gastrointestinal cancer by targeting related molecules in concert with reader proteins. (**A**) ALKBH5 regulates the molecular mechanism of CRC. (**B**) ALKBH5 regulates the molecular mechanism of HCC, ICC, and LCSCs. (**C**) ALKBH5 regulates the molecular mechanism of PC and PDAC. (**D**) ALKBH5 regulates the molecular mechanism of GC. (figure was created with Biorender.com)

can reverse the radiation sensitivity induced by ALKBH5 or YTHDF2 and may serve as a potential target for radiotherapy in CRC [64]. Luo et al. discovered that ALKBH5 is downregulated in CRC. ALKBH5 removes m6A modification on the mRNA of solute carrier family 7 members 11 (SLC7A11), reducing mRNA stability, thereby decreasing SLC7A11 transcription and expression, promoting ferroptosis in CRC cells [65].

In summary, these studies confirm the close association of ALKBH5 with the progression of CRC, suggesting that ALKBH5 may hold significant clinical significance as a target for drug therapy in CRC.

Liver cancer

LC is the sixth most common cancer globally, ranking fourth in mortality among all cancers [66]. Studies suggest that ALKBH5 is highly expressed in hepatocellular carcinoma (HCC) and correlates with poor prognosis in HCC patients. Tumor-associated macrophages (TAMs) play a critical role in establishing the tumor microenvironment. ALKBH5, through an m6A-dependent mechanism, regulates the expression of mitogen-activated protein kinase kinase kinase 8 (MAP3K8), mediating the activation of downstream c-Jun N-terminal kinase (JNK) and extracellular regulated kinase (ERK) pathways, and promoting HCC cell proliferation, migration, and the recruitment of programmed death-ligand 1 (PD-L1)+macrophages [67]. Related studies have reported interactions of ALKBH5 with PD-L1 mRNA in intrahepatic cholangiocarcinoma (ICC). Through the ALKBH5-PD-L1 axis, it maintains the expression of PD-L1 in tumor cells, suppressing T-cell proliferation and cytotoxicity, and regulating the occurrence of ICC [68]. Liver cancer stem cells (LCSCs) are closely associated with the

treatment and recurrence of LC. ALKBH5 regulates the expression of SRY-related HMG box (SOX4) through demethylation, thereby activating the sonic hedgehog (SHH) signaling pathway and promoting the progression of LCSCs [69]. Extracellular vesicles (EVs) play a crucial role in the intercellular transfer of various bioactive substances that promote tumor proliferation, migration, invasion, and development. Han et al. discovered that bone-metastasized HCC-derived EVs (BM-EVs) can promote the progression of HCC by transferring miR-3190 targeting ALKBH5 [70]. Recently, Zhang et al. found that LINC02551 serves as a target of ALKBH5, disrupting the combination between DEAD-box RNA helicase (DDX24) and E3 ubiquitin ligase tripartite motif-containing 27 (TRIM27) to reduce the ubiquitination of DDX24 and subsequent degradation, ultimately promoting HCC growth and metastasis [71].

Some studies suggest that ALKBH5 is downregulated in HCC compared to normal liver cells and may act as a tumor suppressor to inhibit cancer development processes such as proliferation, migration, and invasion in HCC. Therefore, further exploration of the role of ALKBH5 in HCC is warranted. Wang et al. found that ALKBH5 is downregulated in HCC, through interaction with the m6A reader protein IGF2BP1, downregulates the expression of its target gene AdipoQ Receptor 4 (PAQR4) at the transcriptional and translational levels, thereby inhibiting the activation of the PI3K/AKT pathway and the growth of LC [72]. Research indicates that LY6/PLAUR Domain Containing 1 (LYPD1) can act as an oncogene to promote the occurrence and development of HCC. ALKBH5, through an m6A-dependent mechanism, diminishes the expression of LYPD1 and strengthens the inhibitory effect of ALKBH5 on LYPD1 under the recognition and stabilization of IGF2BP1[73]. Hepatic stellate cells (HSCs) can induce radiation-induced liver fibrosis (RILF) under radiotherapy for HCC. ALKBH5 can regulate the hepatic microenvironment and serve as a radiosensitization target for HCC, providing new insights into the radiotherapy and prognosis of HCC [74] (Fig. 3).

Overall, the role of ALKBH5 expression in LC is complex and diverse. It can either promote or inhibit LC progression, and these contradictory findings may be due to different pathways regulated by ALKBH5.

Pancreatic cancer

PC is a prevalent malignancy of the digestive tract, marked by challenging early diagnosis, concealed symptoms, and high mortality, with a 5-year survival rate of less than 10% [75]. Research suggests that ALKBH5 is downregulated in PC. Kaplan-Meier survival analysis demonstrates a significant correlation between low ALKBH5 expression and overall survival in PC patients. ALKBH5 interacts with the YTHDF2 reading protein to upregulate the expression of the period circadian regulator 1 (PER1) gene in an m6A-dependent manner. The upregulation of PER1 activates the P53-related signaling pathway, suppressing the growth of PC cells [76]. Antisense LncRNA is closely linked to tumor development. He et al. discovered that Potassium two pore domain channel subfamily K member 15 and WISP2 antisense RNA 1 (KCNK15-AS1) is downregulated in PC cells and tissues, leading to the suppression of migration and invasion in PC cells. Mechanistically, ALKBH5 enhances the expression of KCNK15-AS1 by demethylating m6A modification. It recruits the proto-oncogene mouse double minute 2 (MDM2) to facilitate the ubiquitination of RE1-silencing transcription factor (REST), leading to the transcriptional upregulation of phosphatase and tension homolog (PTEN) to deactivate the AKT signaling pathway [77, 78]. Iron metabolism plays a crucial role in multiple aspects of cancer cells, including DNA synthesis, mitochondrial respiration, cell proliferation, and the tumor microenvironment. In pancreatic ductal adenocarcinoma (PDAC), ALKBH5 regulates the stability of F-box and leucine-rich repeat protein 5 (FBXL5) RNA. Overexpression of ALKBH5 results in a marked decrease in intracellular iron levels, along with reduced cell migration and invasion capabilities. FBXL5, through the regulation of iron proteins such as iron regulatory protein 2 (IRP2), contributes to the control of PDAC occurrence and progression [79]. Tang and colleagues discovered that overexpression of ALKBH5 enhances the sensitivity of PDAC cells to chemotherapy. Reduced levels of ALKBH5 are linked to poor prognosis in PDAC and various other cancers. ALKBH5 can impact the Wnt signaling pathway, decrease RNA methylation of Wnt inhibitory factor 1 (WIF-1), and inhibit PC tumorigenesis [80]. Studies suggest that ALKBH5-mediated m6A modification results in the upregulation of DNA damage-inducible transcript 4 (DDIT4-AS1) expression in PDAC. DDIT-AS1, by stabilizing DDIT4 and activating the mechanistic target of the rapamycin (mTOR) pathway, enhances cancer stem cells and inhibits chemosensitivity to gemcitabine (GEM) [81]. M6A methylation is closely associated with the tumor hypoxic microenvironment. Methylated RNA immunoprecipitation sequencing (MeRIP-seq) results reveal that histone deacetylase type 4 (HDAC4) is an m6A-targeted gene in the tumor-hypoxic environment, and it modulates the tumor-hypoxic microenvironment through the ALKBH5/HDAC4 /HIF1α pathway [82] (Fig. 3). In summary, ALKBH5 is downregulated in PC, and could influence the growth, migration, invasion, and chemotherapy sensitivity of PC cells through multiple mechanisms.

Gastric cancer

GC is presently among the most common cancers, ranking fifth in the incidence of various cancers [54].

Significant attention should be given to the diagnosis and treatment of GC. Experimental evidence from in vivo and in vitro studies indicates that ALKBH5 is upregulated in GC and correlates with clinical poor prognosis and low survival rates. LINC00659 facilitates the binding and upregulation of ALKBH5 with Janus kinase 1 (JAK1) mRNA in a m6A-YTHDF2-dependent manner, thereby promoting the development of GC [83]. Wang and colleagues discovered that lncRNA NRON is highly expressed in GC and promotes the occurrence and development of GC by binding with demethylase ALKHB5 to mediate Nanog (homeobox domain transcription factor) mRNA decay. It is anticipated to be a prognostic factor and potential therapeutic target for GC patients [84]. Studies suggest a close association between lncRNA NEAT1 and ALKBH5. MeRIP experiments and rescue experiments confirm that ALKBH5 can bind to lncRNA NEAT1, mediating the demethylation process of NEAT1 in an m6A-dependent manner. This process influences the expression of EZH2 (a subunit of the polycomb repressive complex) and contributes to the invasion and metastasis of GC [85]. Bioinformatics results indicate that ALKBH5 acts as an upstream target of Protein kinase, membrane-associated tyrosine/threonine 1 (PKMYT1), negatively regulating PKMYT1 expression. In collaboration with the reading protein IGF2BP3, PKMYT1's mRNA stability is increased. Depletion of ALKBH5 results in the upregulation of PKMYT1 expression, consequently promoting the invasion and migration of GC [86](Fig. 3). In conclusion, the expression of ALKBH5 is upregulated in GC. ALKBH5 promotes the invasion and metastasis of GC cells through various mechanisms, and is associated with poor prognosis and low survival rates of GC patients.

Esophageal squamous cell carcinoma

ESCC is the seventh most common cancer globally, and it stands as the sixth most common cause of cancer-related deaths. Notably, ESCC exhibits high recurrence rates, leading to an unfavorable prognosis over the long term [87]. Xiao et al. discovered reduced expression of ALKBH5 in ESCC. The overexpression of ALKBH5 suppresses the proliferation, migration, and invasion of ESCC cells. Simultaneously, it induces a certain degree of G1 phase arrest in ESCC cells, suggesting that the deficiency in ALKBH5 expression is one of the contributing factors to the malignancy of ESCC tumors. In vivo, experiments confirm that the loss of ALKBH5 significantly inhibits the tumor growth of ESCC cells transplanted subcutaneously in BALB/c nude mice. ALKBH5 acts as an independent prognostic factor for patient survival and is correlated with poor prognosis in ESCC patients [88].

Currently, research on ALKBH5 in ESCC is relatively scarce, and more substantial research is needed for making the role and mechanism clearer.

Future perspectives

In recent years, with the confirmed demethylase activity of ALKBH5 and the rapid development of high-throughput sequencing for m6A methylation, research on the demethylase ALKBH5 has steadily advanced worldwide. The dysregulation of m6A demethylase ALKBH5 is observed in various gastrointestinal cancers and can directly or indirectly function as a regulatory gene in multiple cancers, regulating processes such as tumor cell proliferation, migration, invasion, metastasis, and drug resistance, thereby influencing the progression of cancer. However, it is worth noting that ALKBH5 plays a dual role in inhibiting or promoting cancer development in certain digestive tract tumors. For example, in CRC, ALKBH5 inhibits CRC development by reducing the mRNA stability of PHF20 [54], while lncRNA NEAT1 promotes CRC progression under the demethylation effect of ALKBH5 [57]. This may be related to the heterogeneity of tumors, differences in the clinical samples collected by researchers, differences in research models, and so on. Therefore, further in-depth research and analysis of the genes regulated by ALKBH5 in specific cancers are needed. Additionally, multiple studies indicate that in the process of regulating the occurrence and development of cancer through downstream target genes, reader proteins often play an auxiliary modifying role. Reader proteins enhance the binding ability between ALKBH5 and target genes by regulating the stability of downstream gene mRNA, mediating the demethylation process of target genes. This provides a new direction for the research on the regulatory mechanism of ALKBH5 in cancer and the development of targeted therapeutic drugs that affect tumor progression through the m6A-dependent regulation of related genes.

Conclusions

ALKBH5 has emerged as an important regulator and promising therapeutic target for the treatment of gastrointestinal cancer. However, the current research on the mechanism of ALKBH5 in gastrointestinal cancer is still in the preliminary stage, and there is a significant gap that needs to be filled in understanding the mechanisms of ALKBH5 in regulating metabolism, angiogenesis, and related signaling pathways, which may be the causes of the dual or controversial role of ALKBH5 in gastrointestinal cancer. More efforts in advanced studies will hold great potential and promote our understanding of the role of ALKBH5 in gastrointestinal cancer as well as lead to the development of more effective and personalized treatments for patients with gastrointestinal cancer.

Abbreviations

m6A	N6-methyladenosine
UTRs	Untranslated regions
ALKBH5	AlkB homolog 5
METTL3	Methyltransferase-like 3
METTL14	Methyltransferase-like 14
METTL16	Methyltransferase-like 16
WTAP	Wilms tumor 1 associated protein
ZC3H13	Zinc finger CCCH-type containing 13
RBM15	RNA-binding motif protein 15
VIRMA	Vir-like m6 A methyltransferase-associated
CBLL1	Cbl proto-oncogene like1
Flacc	Fl(2)d-associated complex component
FTO	Fat mass and obesity-associated protein
YTH	YT521-B homology
YTHDF1/2/3	YTH N6-methyladenosine RNA binding protein 1/2/3
YTHDC1/2	YT521-B homology-domain-containing protein 1/2
IGF2BPs	IGF2 mRNA binding protein
IGF2BP1/2	Insulin-like growth factor 2 mRNA binding protein 1/2
HNRNPs	Heterogeneous nuclear ribonucleoproteins
GC	Gastric cancer
CRC	Colorectal cancer
LC	Liver cancer
PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
COAD	Colon adenocarcinoma
HCC	Hepatocellular carcinoma
ICC	Intrahepatic cholangiocarcinoma
LCSCs	Liver cancer stem cells
HSCs	Hepatic stellate cells
ESCC	Esophageal squamous cell carcinoma
DSBH	Double-stranded β-helix fold
HIF-1α	Hypoxia-inducible factor 1α
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B
NF-κB	Nuclear factor-κB
DKK1	Dickkopf-related protein 1
CCL5	C-C motif chemokine ligand 5
PHF20	Plant homeodomain finger protein 20
PKM2	Pyruvate kinase M2
RAB5A	A Rab GTPase family protein
NEAT1	Nuclear paraspeckle assembly transcript 1
FOXO3	Forkhead box O3
SPRY2	Sprouty2
SLC7A11	Solute carrier family 7 members 11
TAMs	Tumor-associated macrophages
MAP3K8	Mitogen-activated protein kinase kinase kinase 8
JNK	C-Jun N-terminal kinase
ERK	Extracellular regulated kinase
PD-L1	Programmed death-ligand 1
SOX4	SRY-related HMG box
SHH	Sonic hedgehog
EVs	Extracellular vesicles
BM-EVs	Bone-metastasized HCC-derived EVs
DDX24	DEAD-box RNA helicase
TRIM27	E3 ubiquitin ligase tripartite motif-containing 27
PAQR4	AdipoQ Receptor 4
PI3K	Phosphatidylinositol 3-kinase
LYPD1	LY6/PLAUR Domain Containing 1
RILF	Radiation-induced liver fibrosis
PER1	Period circadian regulator 1
KCNK15-AS1	K member 15 and WISP2 antisense RNA 1
MDM2	Mouse double minute 2
REST	RE1-silencing transcription factor
PTEN	Phosphatase and tension homolog
FBXL5	F-box and leucine-rich repeat protein 5
IRP2	Iron regulatory protein 2
WIF-1	Wnt inhibitory factor 1
DDIT4-AS1	DNA damage-inducible transcript 4
mTOR	Mechanistic target of rapamycin
GEM	Gemcitabine
MeRIP-seq	Methylated RNA immunoprecipitation sequencing
HDAC4	Histone deacetylase type 4
JAK1	Janus kinase 1
PKMYT1	Protein kinase, membrane associated tyrosine/threonine 1

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Data availability
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 who have contributed to this manuscript have provided their collective agreement for its publication in this journal.

Competing interests
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