Role of the m^{6}A demethylase ALKBH5 in gastrointestinal tract cancer (Review)

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Abstract. N^6-methyladenosine (m^{6}A) is one of the most universal, abundant and conserved types of internal post-transcriptional modifications in eukaryotic RNA, and is involved in nuclear RNA export, RNA splicing, mRNA stability, gene expression, microRNA biogenesis and long non-coding RNA metabolism. AlkB homologue 5 (ALKBH5) acts as a m^{6}A demethylase to regulate a wide variety of biological processes closely associated with tumour progression, tumour metastasis, tumour immunity and tumour drug resistance. ALKBH5 serves a crucial role in human digestive system tumours, mainly through post-transcriptional regulation of m^{6}A modification. The present review discusses progress in the study of the m^{6}A demethylase ALKBH5 in gastrointestinal tract cancer, summarizes the potential molecular mechanisms of ALKBH5 dysregulation in gastrointestinal tract cancer, and discusses the significance of ALKBH5-targeted therapy, which may provide novel ideas for future clinical prognosis prediction, biomarker identification and precise treatment.

Contents

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Abbreviations: m^{6}A, N^6-methyladenosine; ALKBH5, AlkB homologue 5; miRNA/miR, microRNA; lncRNA, long non-coding RNA; circRNA/circ, circular RNA; METTL, methyltransferase like; WTAP, Wilms' tumour-associated protein; VIRMA, vir-like m6A methyltransferase-associated protein; YTH, YT521-B homology; hnRNP, heterogeneous nuclear ribonucleoprotein; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; HNRNPC, heterogeneous nuclear ribonucleoprotein C; IGF2BP, insulin-like growth factor 2 mRNA binding protein; FTO, fat mass and obesity-associated protein; α-KG, α-ketoglutaric acid; ssDNA, single-stranded DNA; ssRNA, single-stranded RNA; DSBH fold, double-stranded β-helical core fold; 2OG, 2-oxoglutarate; GBM, glioblastoma; OC, oesophageal cancer; OSCC, oesophageal squamous cell carcinoma; ceRNA, competing endogenous RNA; GC, gastric cancer; ROS, reactive oxygen species; Hsp70, heat shock protein family A; CRC, colorectal cancer; COAD, colon adenocarcinoma; PHF20, PHD finger protein 20; HK2, hexokinase 2; FABP5, ALKBH5-fatty acid binding protein 5; MDSC, myeloid-derived suppressor cell; BET1L, Bet1 Golgi vesicular membrane trafficking protein-like; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LYPD1, LY6/PLAUR domain containing 1; NAFLD, non-alcoholic fatty liver disease; EMT, epithelial-mesenchymal transition; UBR7, ubiquitin protein ligase E3 component n-recognin 7; PD-L1, programmed death ligand 1; circRNA cIARS, hsa_circ_0008367; SF, sorafenib; FLT-1, fms-like tyrosine kinase-1; HBV, hepatitis B virus; HBV-HCC, HBV-associated HCC; SNAI2, snail family transcriptional repressor 2; HBx, HBV X protein; GBC, gallbladder cancer; FOXA1, forkhead box A1; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; pNET, pancreatic neuroendocrine tumour; GEM, gemcitabine; OS, overall survival; DFS, disease-free survival; PD-1, programmed cell death receptor 1; CELF2, CUGBP Elav-lik family member 2; IRP2, iron-regulatory protein 2; siRNA, small interfering RNA; MV1035, 2-methyl-3-propyl-5H-imidazo[1,2-c][1,3]benzoxazin-5-thione; IOX1, 5-carboxy-8-hydroxyquinolin; NOG, N-oxalylglycine; 20m, 5-hydroxy-1-[4-((N-methylsulfamoyl) methyl)phenyl]-1H-pyrazole-3-carboxylic acid; DDO-2728, 4-(Trifluoromethyl)benzyl 4-(6-(2,6-dihydroxy-3-nitrobenzoyl) pyrazolo[1,5-a]pyrimidin-2-yl)benzoate; ncRNA, non-coding RNA

Key words: m^{6}A, ALKBH5, RNA demethylation, gastrointestinal tract cancer, therapeutic target

1. Introduction

In total, >100 RNA modifications (termed the epitranscriptome) are currently known in living organisms, and are involved in various biological processes that are associated with multiple functions, including adipogenesis, stem cell differentiation and the heat shock response (1,2). Methylation of the N^6 position of adenosine was first identified in eukaryotic mRNAs in the 1970s. This modified base is referred to as N^6-methyladenosine (m^{6}A) (3,4). m^{6}A has been found to be a prevalent and abundant internal modification of a wide range of RNAs, including but not restricted to mRNAs, transfer RNAs, ribosomal RNAs, microRNAs (miRNAs/miRs) and long non-coding RNAs (lncRNAs) (5).

m^{6}A serves a role in physiological and pathological processes. m^{6}A is involved in growth and development (6), DNA damage repair (7), and osteogenic differentiation (8). The dysregulation of pathways controlled by m^{6}A modification may be a key factor in diabetes (9), autoimmune diseases (10), tumours (11) and other diseases. Changes in m^{6}A levels are associated with various cellular processes (12), removal and recognition of m^{6}A modifications on transcripts can affect nuclear RNA export (13), RNA splicing (14), mRNA stability (15), miRNA biogenesis (16), lncRNA metabolism (17) and circular RNA (circRNA/circ) stability (18). m^{6}A modification, a dynamic and reversible RNA modification, is regulated by three types of molecules, namely writers, readers and erasers. m^{6}A methyltransferases (writers) are responsible for adding m^{6}A modifications; m^{6}A recognition proteins (readers) are responsible for recognizing and binding m^{6}A-modified transcripts; and demethylases (erasers) are responsible for removing m^{6}A modifications (19) (Fig. 1).

m^{6}A writers consist of multiple components, including methyltransferase like (METTL)3, METTL14 and Wilms' tumour-associated protein (WTAP) (20). METTL3 and METTL14 perform mammalian cellular m^{6}A methylation-related functions by forming a stable METTL3/METTL14 heterodimer (21). WTAP colocalizes with this complex and interacts with the complex to influence its m^{6}A methylation activity, acting as a regulatory subunit (20,21). These were the earliest known m^{6}A methylases, and novel m^{6}A writers have since been identified; these include METTL16 (22), METTL4 (23), METTL5 (24), RNA-binding motif protein 15 (25), zinc finger CCCH-type containing 13 (26), zinc finger CCHC-type containing 4 (27) and vir-like m^{6}A methyltransferase-associated protein (also known as KIAA1429) (28), which are jointly involved in the regulation of RNA methylation. The YT521-B homology (YTH) family of proteins were the first readers to be identified, and there are five proteins carrying the YTH structural domains in the human genome, which are divided into nuclear [YTH N6-methyladenosine RNA binding protein (YTHD)C1] and cytoplasmic m^{6}A readers (YTHDF1, YTHDF2, YTHDF3 and YTHDC2) (29). There are also other m^{6}A-recognizing proteins, such as heterogeneous nuclear ribonucleoproteins (hnRNPs) (30), namely heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1), heterogeneous nuclear ribonucleoprotein C (HNRNPC), heterogeneous nuclear ribonucleoprotein G and insulin-like growth factor 2 mRNA binding protein 1/2/3 (IGF2BP1/2/3) (31).

Fat mass and obesity-associated protein (FTO) was recognized as the first m^{6}A mRNA demethylase, and the identification of FTO defined the concept of reversible RNA modification (32,33). A second m^{6}A eraser, AlkB homologue 5 (ALKBH5), was subsequently identified (34). FTO and ALKBH5 both belong to the AlkB family of non-heme Fe(II)/α-ketoglutaric acid (α-KG)-dependent dioxygenases (35). They have a function opposite to that of writers; they catalyse the oxidative demethylation of m^{6}A in RNA to remove the m^{6}A modification from RNA (32,34,36). m^{6}A acts as a 'conformational marker' that induces major overall conformational changes in RNA, thereby regulating the substrate specificity of the m^{6}A demethylases FTO and ALKBH5 (37). In terms of substrate selection, FTO tends to catalyse the 3-methylthymine modification of single-stranded DNAs (ssDNAs), the 3-methyluracil modification of single-stranded RNAs (ssRNAs) and the m^{6}A modification of ssRNAs (32,38). The unique loop in FTO (residues 210-223) and the short loop between β2 and β3 (residues 85-88) contribute to the recognition of the sequence and structure of the RNA substrate. Compared with FTO, ALKBH5 has a different structural conformation at this position when it binds to nucleic acids, and thus, has a more stringent substrate selection preference, catalysing only m^{6}A ssDNA and m^{6}A ssRNA modifications (34,38-40).

2. ALKBH5

Chen *et al* (41), Aik *et al* (35), Feng *et al* (40) and Xu *et al* (42) reported the crystal structures of zebrafish ALKBH5 and human ALKBH5, which improved the understanding of the substrate selectivity and different demethylation mechanisms of AlkB family proteins. Zhou and Han (36) reported the cloning, protein expression and purification, crystallization, and X-ray data collection of ALKBH5 to provide insights into the potential mechanism of its specific substrate selection. Purslow *et al* (43) examined the conformational dynamics of ALKBH5 in solution, providing the first atomic-resolution model of the ALKBH5 protein in its disordered conformational state. The aforementioned study provides biochemical data support for the future analysis of the conformational dynamics of ALKBH5 in determining its activity and selectivity.

ALKBH5 belongs to the non-heme Fe(II)/α-KG-dependent dioxygenase AlkB family of proteins, and the human AlkB family has nine members, including ALKBH1-8 and FTO (44). α-KG-dependent dioxygenases are an extended superfamily of enzymes that catalyse a wide range of oxidative reactions; these enzymes share the same double-stranded β-helical core fold (DSBH fold), although they act on different substrates and have conserved 2-oxoglutarate (2OG; also known as α-KG) and Fe^{2+} binding sites (45,46). ALKBH5, similar to other AlkB family proteins, binds 2OG and a metal cofactor (Fe^{2+}) in a conserved manner (35,42). The core of the ALKBH5 catalytic structural domain consists of the typical conserved DSBH fold, which consists of a total of 11 β-strands and 7 α-helices (42) (Fig. 2). The different substrate specificities of different AlkB proteins are determined by the composition of the external secondary structural elements of the conserved DSBH fold, with the most notable structural difference being the so-called 'nucleotide recognition lid', which is unique to the AlkB protein subfamily (47). The cap region is further

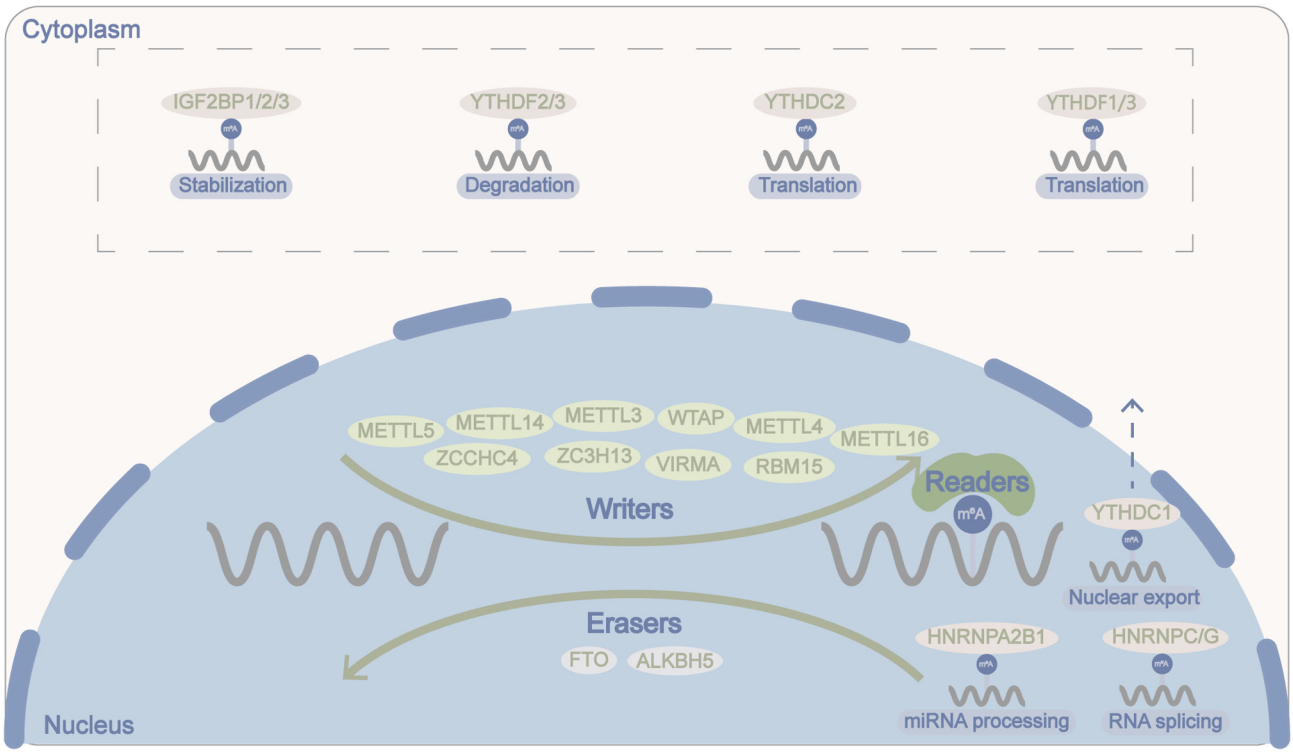

Figure 1. Molecular mechanism of m^{6}A mediated by writers, erasers and readers. m^{6}A methyltransferases (writers) are responsible for installing m^{6}A modifications, including METTL3, METTL14, WTAP, RBM15, VIRMA, METTL16, METLL4, METTL5, ZCCHC4 and ZC3H13. FTO and ALKBH5 are demethylases (erasers), which are responsible for removing m^{6}A modifications. m^{6}A recognition proteins (readers) are responsible for recognizing and binding m^{6}A-modified transcripts, which regulate nuclear export, RNA splicing, stabilization, degradation and translation. m^{6}A, methyladenosine; METTL, methyltransferase like; WTAP, Wilms' tumour-associated protein; RBM15, RNA-binding motif protein 15; VIRMA, vir-like m^{6}A methyltransferase-associated protein; ZCCHC4, zinc finger CCHC-type containing 4; ZC3H13, zinc finger CCCH-type containing 13; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homologue 5; IGF2BP, insulin-like growth factor 2 mRNA binding protein; YTHD, YTH N6-methyladenosine RNA binding protein; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; miRNA, microRNA; HNRNP, heterogeneous nuclear ribonucleoprotein.

classified into two sections, Flip1 (residues 117-129) and Flip2 (residues 136-165) (48). Compared with those of ALKBH2 and FTO, the Flip1 region of ALKBH5 has an uncovered and relatively large space in the active site, and the Flip2 region is highly flexible (42). The unique composition and conformation of these regions may confer unique substrate-selective features to ALKBH5 (40). In addition, the unique disulfide bond structure (between residues Cys-230 and Cys-267) of ALKBH5 is highly conserved only among different species of ALKBH5 proteins, which prevents double-stranded DNA and double-stranded RNA from accessing the active site of ALKBH5 and determines the binding preference of ALKBH5 for single-stranded substrates (40,42).

Endogenous ALKBH5 is predominantly found in the nucleus, where it colocalizes with nuclear speckles, and is less abundant in the cytoplasm (34). Nuclear speckles are integrally regulated nuclear bodies that promote gene expression, and >30 nuclear speckled proteins serve crucial roles in both transcription and splicing (49). The demethylation activity of ALKBH5 affects mRNA export, RNA splicing, mRNA stability, gene expression and the assembly of mRNA processing factors in nuclear speckles (34,50). Under normal physiological conditions, ALKBH5 is highly expressed in the lungs, followed by the testis, pancreas, spleen and ovaries (51). ALKBH5 serves a key role in meiosis, and has been found to participate in spermatogenesis (34), skeletal muscle development (52), learning and memory (53), and other biological behaviours. ALKBH5 is involved in osteoarthritis (54), pulmonary fibrosis (55), stroke (56), systemic lupus erythematosus (57) and diabetes (58) as an important biomolecule. In addition, ALKBH5 is closely associated with a variety of tumours.

3. Dual role of the ALKBH5 gene in digestive tract tumours

ALKBH5 has been extensively studied in a variety of tumours, such as glioblastoma (GBM) (59), head and neck squamous cell carcinoma (60), colorectal cancer (CRC) (61), ovarian carcinoma (62), cervical cancer (63), acute myeloid leukaemia (AML) (64), breast cancer (65), melanoma (66), hepatocellular carcinoma (HCC) (67), and lung cancer (68), and serves a role in tumour growth (69), tumour metastasis (70), tumour immunity (71), tumour drug resistance (62) and tumour metabolism (72). ALKBH5 has been shown to act through several important pathways, including the PI3K/AKT (73), Janus kinase 1 (JAK1)/STAT3 (74), Wnt (75), NF-κB (76) and mTOR (77) pathways. However, the potential mechanism of ALKBH5 in cancer has not been fully investigated and is controversial. ALKBH5 serves dual roles in different types of cancer as either a tumour promoter or a tumour suppressor (78,79) and occasionally serves both pro- and antigenic roles in the same type of cancer (67,80) (Fig. 3; Table SI). The molecular mechanism of ALKBH5 needs to be further investigated.

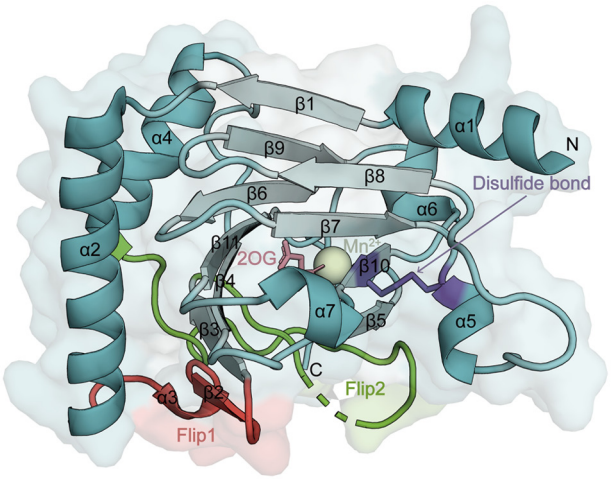

Figure 2. Overall structure of the human ALKBH5 catalytic domain (amino acids 77-293). Cartoon representation of the ALKBH5 catalytic domain in the presence of 2OG and Mn^{2+} (Protein Data Bank ID: 4OCT). The secondary structural elements are labelled α1-α5 for helices (α1-α2 and α4-α5 coloured blue, α3 coloured red) and β1-β11 for strands (β1 and β3-β11 coloured grey, β2 coloured red). The Mn^{2+} ion is shown as a grey-yellow sphere. Mn^{2+} is a substitute for Fe^{2+}. The disulfide bond between Cys-230 and Cys-267 is highlighted in purple.2OG is highlighted in pink. The disulfide bond as well as 2OG are shown as sticks. Flip1 and Flip2 are shown in red and green, respectively. The figure was generated using Pymol Version 2.6.0a0. (182). ALKBH5, AlkB homologue 5; 2OG, 2-oxoglutarate.

The present review focuses on the research progress regarding the role of ALKBH5 in digestive system tumours, paying attention to the regulatory roles of different targets of ALKBH5, as well as the current research status of small-molecule inhibitors targeting ALKBH5.

Oesophageal cancer (OC). OC is a highly malignant tumour of the digestive system, and most cases are diagnosed at advanced stages, resulting in a high recurrence rate and poor prognosis (81). OC is the eighth most commonly diagnosed cancer and the sixth most common cause of cancer-related deaths worldwide (82). The incidence and mortality rates of OC vary by sex, and it is more common in male patients than in female patients (82). The major histologic subtypes of OC include oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma, of which OSCC is the most common squamous-cell carcinoma (83). Currently, the biological role and regulatory mechanism of ALKBH5 in OC have been less well studied than those in other digestive system cancers, and research progress is relatively limited (73,84-90).

Reduced ALKBH5 expression, which is frequently detected in OC tissues, accelerates OC cell proliferation, migration and invasion (91). Chen *et al* (92) reported that ALKBH5 inhibited miR-194-2 through m^{6}A demethylation, promoted RAI1 expression, activated the Hippo signalling pathway and inhibited Yes associated protein/tafazzin function to prevent the malignant behaviour of OC. Xue *et al* (93) reported a positive feedback loop between miR-193a-3p and ALKBH5, which decreased the expression of ALKBH5 in OC, and promoted the growth and metastasis of OC. Qiao *et al* (94) reported that serine hydroxymethyltransferase 2 regulated the stability of c-myc mRNA through METTL3/FTO/ALKBH5/IGF2BP2-mediated m^{6}A modification, thereby promoting the malignant progression of OC with immune escape.

Some researchers have proposed the opposite, suggesting that ALKBH5 promotes the progression of OC and acts as a tumour-promoting factor (95,96). Nagaki *et al* (95) reported that ALKBH5 downregulated p21 expression and regulated the cell cycle to promote the proliferation of OC cells. At present, the mechanisms of m^{6}A modification and regulation of lncRNAs in tumours are as follows: m^{6}A can cause structural remodelling of lncRNAs, thus affecting the interaction of lncRNAs with proteins regulating RNA-protein interactions (97); m^{6}A promotes transcriptional repression induced by lncRNAs (25); lncRNAs act as competing endogenous RNAs (ceRNAs) under m^{6}A modification regulation, regulating miRNA expression and biological functions (98); and m^{6}A is involved in regulating the stability of lncRNA transcripts (96). Wu *et al* (96) reported that ALKBH5 stabilized the lncRNA CASC8 transcript and induced the upregulation of the lncRNA CASC8, which activated the Bcl2/caspase3 pathway by stabilizing the expression of heterogeneous nuclear ribonucleoprotein L, thus promoting the progression of OC and reducing the sensitivity of OC cells to cisplatin.

Gastric cancer (GC). GC is one of the most important malignant tumours globally and is characterized by high lethality (99). GC ranks fifth in global incidence and fourth in mortality among all cancer types, with an incidence rate in men that is twice as high as that in women (82,100). The World Health Organization histologic classification of GC includes stomach adenocarcinoma, gastric squamous cell carcinoma, gastric adenosquamous carcinoma, gastric undifferentiated carcinoma, gastroblastoma and gastric neuroendocrine neoplasms, with the vast majority of GCs being adenocarcinomas (83). Emerging studies have reported the important role of m^{6}A modifications in GC, and the molecular mechanisms of dysregulated m^{6}A modifications and abnormalities in GC have received increasing attention; however, the function of ALKBH5 in GC remains controversial (70,84,85,101).

ALKBH5 is commonly highly expressed in GC, and high ALKBH5 expression promotes the proliferation, invasion and migration of GC cells both *in vivo* and *in vitro* (78,84,102). High ALKBH5 expression is related to a poor prognosis in patients with GC (74). Bioinformatics analysis revealed that ALKBH5 may be a key gene influencing the immune microenvironment of GC and regulating the progression of GC (103). Specifically, with respect to the molecular mechanism, the upregulation of ALKBH5 expression in GC is involved in the invasion and migration of GC cells through the regulation of the lncRNA NEAT1, which acts as a scaffold and affects the expression of downstream genes by regulating enhancer of zeste 2 polycomb repressive complex 2 subunit (84). Wang *et al* (85) showed that the lncRNA NRON interacts with ALKBH5 to increase the mRNA stability and expression of Nanog, which serves an oncogenic role in GC. Fang *et al* (104) found that ALKBH5 suppressed the m^{6}A modification of the lncRNA TP53TG1, reduced lncRNA TP53TG1 stability, inhibited the binding of the lncRNA TP53TG1 to cellular inhibitor of PP2A and its ubiquitination-mediated degradation, and promoted the activation of the PI3K/AKT pathway, thereby promoting GC progression. ALKBH5, which is regulated

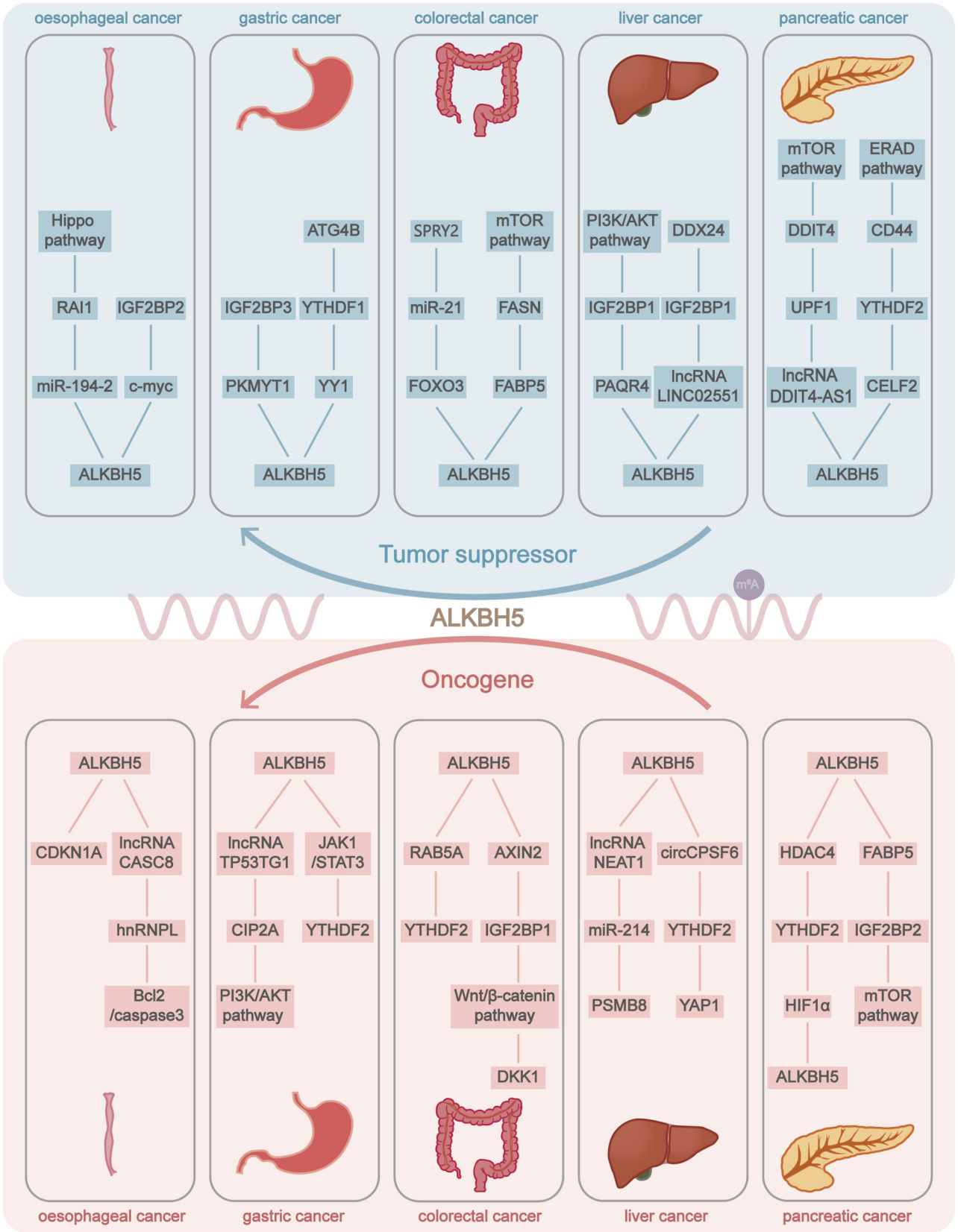

Figure 3. Biological functions and molecular mechanisms of ALKBH5 in gastrointestinal tract cancers. ALKBH5 serves dual roles as either a tumour promoter or a tumour suppressor in oesophageal cancer, gastric cancer, colorectal cancer, liver cancer and pancreatic cancer. ALKBH5, AlkB homologue 5; lncRNA, long non-coding RNA; miR, microRNA; LINC, long-integrated non-coding; ERAD, endoplasmic reticulum-associated degradation; circ, circular RNA.

by long-integrated non-coding (LINC)00659, upregulates JAK1 expression, activates the JAK1/STAT3 pathway, and promotes the proliferation and migration of GC cells (74). Chen *et al* (78) found that ALKBH5 downregulated ChaC

glutathione specific gamma-glutamylcyclotransferase 1 expression by erasing the m^{6}A modification, disrupted reactive oxygen species (ROS) homeostasis in GC, attenuated the chemosensitivity of GC cells, and promoted GC development and metastasis. Exposure to the environmental carcinogen N-nitroso compounds activates ALKBH5-zinc finger with KRAB and SCAN domains 3-YTHDF2-VEGFA signalling, promoting malignant progression of GC (102). Upregulation of ALKBH5 expression enhances circFOXP1 expression by mediating the m^{6}A modification level of circFOXP1 in GC, thereby regulating SOX4 expression and miR-338-3p to promote the progression of GC (105). Suo *et al* (106) noted that the heat shock protein family A (Hsp70) member 4/ALKBH5/CD58 axis reduced cytotoxicity of CD8$^+$T cell, inducing immune escape in GC cells.

However, it has also been reported that ALKBH5 expression is decreased in GC and that high ALKBH5 expression can predict a favourable prognosis, inhibit GC carcinogenesis and metastasis, and act as a tumour suppressor (70,101,107). Bioinformatics analysis revealed that ALKBH5 serves an antitumour role in GC and is a potential prognostic marker and immunotherapy target for GC (101). Hu *et al* (70) found that ALKBH5-IGF2BP3 upregulated the expression of PKMYT1 in an m^{6}A-dependent manner, inhibiting the invasion and migration of GC cells. ALKBH5 negatively regulates YY1, thereby inhibiting the activation of the autophagy related 4B cysteine peptidase-dependent autophagy pathway and serving a protective role in GC development (107).

CRC. CRC is the third most prevalent cancer worldwide and the second leading cause of cancer-related deaths (82). It is the second most common type of cancer diagnosed in women and the third most common type of cancer in men (82). The onset of CRC is insidious, with symptoms often not presenting until it reaches an advanced stage, and effective cancer screening measures can reduce the incidence and mortality of CRC (108). Although research on CRC has made great progress, the specific molecular mechanisms that influence tumorigenesis and development remain elusive. Numerous studies have reported that ALKBH5-mediated m^{6}A modification serves a role in CRC progression (61,69,109,110).

Histologic subtypes of CRC include colorectal adenocarcinoma and neuroendocrine tumours, with colon adenocarcinoma (COAD) being the most common type (83). Bioinformatics analysis revealed that ALKBH5 expression is downregulated in CRC, downregulation of ALKBH5 is associated with distant metastasis and the clinicopathological features of CRC and high ALKBH5 expression enhances immune infiltration (111). ALKBH5, which acts as a tumour suppressor in CRC (111,112), has been suggested to be independently associated with prognosis. ALKBH5 can suppress the growth and metastasis of CRC through various pathways and molecular mechanisms. For example, Zhang *et al* (109) reported that ALKBH5 targeted the PHD finger protein 20 (PHF20) m^{6}A modification, downregulated PHF20 expression and inhibited CRC progression. Luo *et al* (110) found that ALKBH5 removed the m^{6}A modification of solute carrier family 7 member 11 mRNA and suppressed its transcription, and that upregulation of ALKBH5 expression promoted ROS release and ferroptosis in CRC. ALKBH5 can also promote CD8$^+$ T-cell infiltration in the CRC tumour microenvironment via the NF-κB-C-C motif chemokine ligand 5 axis, attenuating the malignant behaviour of CRC (113). Furthermore, Wu *et al* (114) reported that ALKBH5 inhibited the proliferation and migration of CRC cells, and exerted antitumour effects by regulating the FOXO3-miR-21-sprouty RTK signaling antagonist 2 axis. Yan *et al* (115) revealed that ALKBH5 and YTHDF1 might affect the immune architecture of COAD and that high ALKBH5 expression with low YTHDF expression might enhance the infiltration of immune cells and improve the immunotherapeutic efficacy of patients with colorectal adenocarcinoma. ALKBH5 can also serve a tumour suppressor role in CRC by regulating the tumour glycolysis pathway, downregulating the expression of jumonji domain containing 8 in an m^{6}A-dependent manner, and inhibiting glycolysis by suppressing the enzymatic activity of pyruvate kinase M1/2 (86). Ye *et al* (116) demonstrated that in obese patients with CRC, the downregulation of ALKBH5 and FTO synergistically negatively regulated the expression of hexokinase 2 (HK2), a key enzyme in glycolysis, in an m^{6}A-IGF2BP2-dependent manner, activating the FOXO signalling pathway and promoting glucose metabolism, which in turn increased the proliferative capacity of CRC cells. Ye *et al* (87) demonstrated that the ALKBH5-fatty acid binding protein 5 (FABP5)-fatty acid synthase-mTOR axis inhibited tumour progression by affecting lipid metabolism and autophagy in CRC. Shao *et al* (117) revealed that ALKBH5 increased the sensitivity of CRC cells to radiotherapy and that the ALKBH5-circAFF2-YTHDF2-cullin associated and neddylation dissociated 1-Cullin1/NEDD8 axis was a potential chemotherapeutic target for CRC. ALKBH5 is downregulated in mutant p53-induced CRC and promotes CRC progression through the p53-ALKBH5-lncRNA CARMN-YTHDF2/YTHDF3-miR-5683-fibroblast growth factor 2-Akt/mTOR pathway (118). Feng *et al* (119) reported that ALKBH5 could affect the immunosuppressive function of myeloid-derived suppressor cells (MDSCs) in CRC by regulating arginase 1 expression, and could inhibit the progression of CRC.

However, Zhai *et al* (61) concluded that high ALKBH5 expression was related to a poor prognosis in CRC and that ALKBH5 acted as a proto-oncogene in CRC. The authors reported that ALKBH5 and IGF2BP1 decreased axin 2 expression in an m^{6}A-dependent manner and facilitated the activation of the Wnt/β-catenin signalling pathway via the expression of dickkopf WNT signaling pathway inhibitor 1, which induced the accumulation of suppressive MDSCs in CRC, and decreased the antitumour activity of natural killer and CD8$^+$ T cells. Furthermore, Shen *et al* (69) showed that ALKBH5 increased RAB5A expression in an m^{6}A-YTHDF2-mediated manner, promoting the proliferation and invasion of CRC cells. Guo *et al* (120) revealed that ALKBH5 upregulated lncRNA NEAT1 expression in colon cancer through methylation and promoted colon cancer progression. Fatty acid anabolism is considered to be related to prostate cancer (121), glioblastoma (122), ovarian cancer (123), lung cancer (124), breast cancer (125) and liver cancer (126) and is known as a novel therapeutic target. Sun *et al* (127) reported that ALKBH5 upregulated the expression of carnitine palmitoyltransferase 1A by removing its m^{6}A modification, and promoted

macrophage fatty acid metabolism with alternatively activated M2 macrophage polarization, accelerating the malignant progression of CRC. ALKBH5 increases the expression of Bet1 golgi vesicular membrane trafficking protein like (BET1L) in an m^{6}A-mediated manner, and BET1L participates in the tumorigenesis and progression of CRC by regulating the steroid biosynthesis-related pathway (128).

Liver cancer and gallbladder cancer (GBC). Primary liver cancer is one of the most common malignancies of the digestive system, the sixth most common type of cancer and the third leading cause of cancer-related deaths worldwide (82). The incidence of liver cancer differs between sexes. The incidence and mortality rates in men are 2 to 3-fold higher than those in women. In men, liver cancer ranks fifth in terms of incidence rate and second in terms of mortality rate among tumours (82). Primary liver cancer includes HCC and intrahepatic cholangiocarcinoma (ICC), as well as other rare types. HCC is the most common primary malignancy of the liver, accounting for >80% of all liver cancer cases, and has a high mortality rate (129). An increasing number of studies have reported the dysregulation of the m^{6}A modification in HCC and the regulatory mechanisms of m^{6}A-related molecules, revealing the role of m^{6}A in HCC (67,73,88,130).

ALKBH5 has been identified as a tumour suppressor in HCC, suppresses tumour growth and metastasis in HCC, and is a prognostic factor in HCC, predicting favourable clinical outcomes (67,73). Chen *et al* (67) reported that ALKBH5-IGF2BP1-mediated m^{6}A modification led to post-transcriptional repression of LY6/PLAUR domain containing 1 (LYPD1) and that dysregulation of the ALKBH5/LYPD1 axis promoted the malignant behaviour of HCC cells. ALKBH5, together with IGF2BP1, downregulates the expression of progestin and AdipoQ Receptor family member 4 in an m^{6}A-dependent manner and inhibits the activation of the PI3K/AKT pathway, thereby suppressing the malignant progression of HCC cells (73). Zhang *et al* (131) reported that ALKBH5 in HCC regulated the decay of lncRNA LINC02551 mediated by IGF2BP1 recognition in an m^{6}A-dependent manner, reduced the expression of the lncRNA LINC02551 and facilitated the degradation of DEAD-box helicase 24, thereby inhibiting epithelial-mesenchymal transition (EMT) in HCC. With the global increase in type 2 diabetes mellitus and obesity, non-alcoholic fatty liver disease (NAFLD) is becoming an increasingly significant risk factor for HCC (132). ALKBH5 promotes the expression of the lncRNA LINC01468, which mediates lipid metabolism, and promotes chemoresistance and tumour progression in NAFLD-associated HCC (133). ALKBH5, as a tumour suppressor, regulates ubiquitin protein ligase E3 component n-recognin 7 (UBR7) in an m^{6}A-dependent manner, and UBR7 inhibits aerobic glycolysis in HCC cells by regulating the Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2-BTB domain and CNC homolog 1-HK2 axi (134).

However, some studies have reported an opposite role for ALKBH5. You *et al* (88) revealed that ALKBH5 promoted the proliferation, invasion and migration of HCC cells via the ALKBH5-MAP3K8 axis, and facilitated the activation of the ERK/JNK signalling pathway to regulate the recruitment of macrophages expressing programmed death ligand 1 (PD-L1). Chang *et al* (130) reported that ALKBH5 affected HCC progression by positively regulating TELO2 interacting protein 1. The connection between ALKBH5 and the circRNA cIARS (hsa_circ_0008367), the circRNA with the highest relative expression in sorafenib (SF)-treated HCC cells, is a vital mechanism of ferroptosis in SF-treated HCC cells (135). Adjibade *et al* (136) demonstrated that the ALKBH5/FTO-activating transcription factor 4 axis was a novel factor promoting resistance to SF in the treatment of HCC. ALKBH5 upregulates the expression of the lncRNA NEAT1 via m^{6}A demethylation, and the lncRNA NEAT1 modulates the expression of proteasome 20S subunit β8 through miR-214, which promotes the growth and migration of HCC (137). Upregulation of lncRNA CASC11 increases the stability and expression of ubiquitin conjugating enzyme E2 T mRNA through ALKBH5-mediated m^{6}A modification, thus promoting the proliferation, migration and invasion of HCC cells (80). Circ-CCT3 promotes the tumorigenesis, metastasis and angiogenesis of HCC via the Circ-CCT3-miR-378a-3p-fms-like tyrosine kinase-1 (FLT-1) regulatory axis via ALKBH5- and METTL3-mediated m^{6}A modifications (138). The m^{6}A demethylation of circCPSF6 is regulated by ALKBH5/YTHDF2, and dysregulation of the circCPSF6-Yes1 associated transcriptional regulator axis is closely related to the malignant behaviour of HCC (139).

Hepatitis B virus (HBV) infection is considered to be an important risk factor for HCC (140), and the clarification of the molecular mechanisms of HBV-associated HCC (HBV-HCC) and identification of potential biomarkers are crucial for clinical diagnosis and accurate treatment. A recent study has shown that ALKBH5 expression is increased in HBV-positive HCC cells, and that HBV promotes the maintenance of HBV-HCC stemness and immune escape by stabilizing snail family transcriptional repressor 2 (SNAI2) transcripts and increasing the number of ligands for the immune checkpoint CD155 through the ALKBH5-SNAI2-YTHDF2 axis (141). The HBV X protein (HBx) induces HBV-associated aberrant epigenetic modifications that promote hepato-carcinogenesis (142). Qu *et al* (143) reported that high ALKBH5 expression predicted a poor prognosis in patients with HBV-HCC and that the HBx-ALKBH5 positive feedback loop through the HBx-WD repeat domain 5-trimethylated H3 lysine 4-ALKBH5 axis was involved in the development of HBV-HCC.

ICC is the second most common primary malignancy of the liver and has a markedly higher recurrence rate than HCC (144). Several studies have reported that high ALKBH5 expression in patients with ICC is closely related to poor outcomes (145,146). Gao *et al* (145) reported that ALKBH5 serves a role in maintaining the stemness and progression of ICC via BUB1 mitotic checkpoint serine/threonine kinase B. Qiu *et al* (146) suggested that ALKBH5-YTHDF2 specifically modulated PD-L1 expression and suppressed T-cell-mediated antitumour immunity in ICC.

GBC is the most common malignant tumour of the biliary tract, and early diagnosis and detection of GBC can improve the survival rate of patients with GBC (147). Chronic inflammation has been shown to be a driving factor of GBC, with cholelithiasis being the most important risk factor (148). ALKBH5 in GBC has been investigated in relatively few

studies; only a single study has shown that TGFβ1 negatively regulates the translation efficiency of forkhead box A1 (FOXA1) by inhibiting the binding ability of ALKBH5 to the FOXA1 coding sequence region, thereby promoting metastasis in GBC with EMT (149).

Pancreatic cancer (PC). PC is a highly malignant gastrointestinal tumour that is difficult to diagnose and treat and has poor survival outcomes. PC is the seventh leading cause of cancer-related mortality worldwide, and due to its poor prognosis, PC accounts for almost as many deaths (466,000) as cases (496,000) (82). However, to the best of our knowledge, the molecular mechanisms underlying the high mortality rate of PC have not yet been clarified. Thus, identifying the key molecular mechanisms that influence the progression of PC is important in the subsequent selection of therapeutic strategies for PC and in improving the survival of patients with PC.

The histologic classifications of PC include pancreatic ductal adenocarcinoma (PDAC), pancreatic neuroendocrine tumours (pNETs) and solid pseudopapillary tumours of the pancreas, and PDAC is the most common type of PC (83). Gemcitabine (GEM) is the first-line chemotherapy for patients with PC, and adjuvant chemotherapy with GEM has been proven to improve the overall survival (OS) and disease-free survival (DFS) of patients with PC (150). However, GEM resistance is an impediment to first-line chemotherapy for PDAC (151), and investigating the mechanisms underlying GEM resistance and increasing the sensitivity of PC cells to GEM is crucial. Emerging studies have demonstrated that ALKBH5 can increase the sensitivity of PC cells to GEM chemotherapy and suppress the progression of PC (75,77,89). ALKBH5 was downregulated in a GEM-treated patient-derived xenograft model, and upregulation of ALKBH5 expression inhibited Wnt signalling by downregulating the m^{6}A modification of WNT inhibitory factor 1, which sensitized PDAC to chemotherapy (75). In addition, low ALKBH5 expression increased the m^{6}A modification of lncRNA SH3BP5-AS1, promoted the recognition of lncRNA SH3BP5-AS1 by IGF2BP1, improved the stability and expression of lncRNA SH3BP5-AS1, activated the Wnt signalling pathway, and upregulated the expression of C-terminal binding protein 1, which led to GEM resistance and promoted the invasion, migration and stemness of PC cells (89). The stability of the lncRNA DDIT4-AS1 is maintained by the m^{6}A modification site and ALKBH5 mediates the demethylation of the lncRNA DDIT4-AS1, downregulates the level of the lncRNA DDIT4-AS1, and inhibits the phosphorylation of UPF1, the degradation of DDIT4 mRNA and the activation of the mTOR pathway, thereby inhibiting the stemness characteristics of PDAC cells and increasing the chemosensitivity of tumour cells to GEM (77).

Bioinformatics predictions have revealed that ALKBH5 expression is strongly associated with the infiltration of immune cells (152), OS and DFS (153) in PC. Guo *et al* (79) reported that low ALKBH5 expression was related to a poor overall prognosis and clinicopathological features in patients with PC, and the specific mechanism was that the lack of ALKBH5 expression inhibited the activation of ALKBH5-period circadian regulator 1-ATM-checkpoint kinase 2-P53/cell division cycle 25C signalling in a manner dependent on m^{6}A-YTHDF2, which promoted the migration and invasion of PC cells. It has been reported that ALKBH5 suppresses PC cell motility by demethylating the lncRNA KCNK15-AS1 (154). The lncRNA KCNK15-AS1 also inhibits the malignant behaviour of PC cells by modulating KCNK15 and PTEN to activate the AKT pathway in PC cells (90). Lai *et al* (155) pointed out that ALKBH5 positively regulates CUGBP Elav-like family member 2 (CELF2) in PC, and CELF2 mediates CD44 alternative splicing to affect the endoplasmic reticulum-associated degradation signalling pathway, which regulates the stemness and apoptosis of PC cells, and inhibits their proliferation and metastasis. Huang *et al* (156) showed that ALKBH5 can also target iron metabolism regulators through the ALKBH5-F-box and leucine rich repeat protein 5-iron-regulatory protein 2 (IRP2)/SNAI1 axis in PC. In addition, PC is considered the most hypoxic tumour among solid tumours (157), and under hypoxic conditions, the ALKBH5-histone deacetylase 4-hypoxia-inducible factor-1α positive feedback loop promotes glycolysis and migration in PC cells (72).

pNETs are the second most common malignancy of the pancreas, with increasing incidence (158); however, the role of ALKBH5 in pNETs is largely undefined. Chen *et al* (159) demonstrated that upregulated ALKBH5 increased FABP5 expression in an m^{6}A modification-dependent manner, which activated the PI3K/AKT/mTOR signalling pathway, thus promoting lipid metabolism and malignant behaviour in pNETs.

4. Potential clinical applications of ALKBH5

Diagnostic and prognostic biomarkers. Chen *et al* (92) revealed that ALKBH5 could predict a favourable prognosis in patients with OC. Bioinformatics analysis revealed that decreased ALKBH5 expression increased the risk scores of patients with OC, and the combination of HNRNPA2B1 and ALKBH5 had greater predictive value than ALKBH5 one-gene prognostic signature (160). Xu *et al* (161) reported that a two-gene prognostic signature consisting of HNRNPC and ALKBH5 showed prognostic significance for OC. Fang *et al* (74) revealed that ALKBH5 was a poor prognostic factor and was associated with aggressive disease features in patients with GC. Xu *et al* (103) noted that FTO and ALKBH5 could predict the OS of patients with GC. Xie *et al* (162) found that m^{6}A RNA of peripheral blood had value as a non-invasive diagnostic marker and therapeutic target for patients with CRC, and the slight downregulation of ALKBH5 in these patients might explain the elevated RNA m^{6}A levels in the peripheral blood. Furthermore, ALKBH5 is an independent prognostic factor associated with a favourable prognosis and has guiding significance for the selection of treatments for patients with CRC (112,163). Chen *et al* (67) reported the independent prognostic significance of ALKBH5 in patients with HCC; however, You *et al* (88) had opposite views, and reported that ALKBH5 was a poor prognostic factor. In addition, Nakagawa *et al* (164) were the first to suggest that low ALKBH5 expression in adjacent tissues of patients with HCC was closely related to poorer recurrence-free survival than high ALKBH5 expression in adjacent tissues of patients with HCC and could be used to predict the malignant potential of HCC after resection. Qu *et al* (143) revealed that ALKBH5

was a risk factor affecting prognosis and a potential therapeutic target for HBV-HCC. Bioinformatics analysis has indicated that the expression levels of ALKBH5 were closely associated with clinical outcomes and clinicopathological features, and were an independent prognostic indicator for PC (153,165). Furthermore, Lin *et al* (166) reported that the ALKBH5 copy number variation was associated with worse OS and DFS than those with diploid genes in patients with PC. Xu *et al* (167) reported that ALKBH5 was negatively associated with clinal stage, and Zhang *et al* (152) revealed that high ALKBH5 expression was associated with advanced PC.

Treatment with ALKBH5. Wu *et al* (86) synthesized ALKBH5 mRNA-loaded folic acid-modified exosome-liposome hybrid nanoparticles, providing a preclinical approach for the application of ALKBH5 mRNA nanotherapy for CRC. Emerging research has suggested that the combination of vesicle-like nanoparticle-encapsulated ALKBH5 small interfering RNA (siRNA) and anti-programmed cell death receptor 1 (PD-1) therapy is a promising strategy for increasing the sensitivity of CRC to immunotherapy (61).

Small-molecule inhibitors of ALKBH5. The m^6A demethylation activity of the demethylase ALKBH5 is dependent on 2OG and Fe^{2+}, and several studies have reported searches for novel small-molecule inhibitors of ALKBH5, which have been identified mainly by screening marketed drug libraries or by high-throughput virtual screening of 2OG analogues and related compounds (40,168,169). Numerous compounds targeting ALKBH5 have been shown to inhibit its activity in glioblastoma, melanoma and acute myeloid leukaemia, providing evidence to support the selection of the m^6A demethylase ALKBH5 as an anticancer drug target (Table SII) (168-170). However, effective and highly selective ALKBH5 inhibitors are still lacking, and novel potential candidates deserve further exploration.

Several 2OG analogues have been found to exhibit suppressive effects on ALKBH5. Takahashi *et al* (168) screened two novel compounds, Ena15 (IC_{50}, 18.3±1.8 μM) and Ena21 (IC_{50}, 15.7±1.0 μM), which specifically inhibited ALKBH5 according to high-throughput screening. Of these, Ena15 was the first reported non-competitive inhibitor that targets not only ALKBH5 but also other AlkB family proteins, while Ena21 is a more common 2OG competitive inhibitor, and both Ena15 and Ena21 inhibited GBM growth and arrested the cell cycle at the G_0/G_1 phase (168). In a drug repurposing study, Malacrida *et al* (171) performed proteomics and found that 2-methyl-3-propyl-5H-imidazo[1,2-c][1,3]benzoxazin-5-thione (MV1035) could target and inhibit ALKBH5, negatively regulate the expression of CD73, and markedly suppress the migration and invasion of GBM cells. 5-carboxy-8-hydroxyquinoline (IOX1) (IC_{50}, 2.9±0.3 μM), a broad-spectrum 2OG inhibitor, also competitively suppresses the activity of ALKBH5 (172). Tang *et al* (173) found that IOX1 delayed GBM tumour growth and increased the efficacy of anti-PD-1 therapy by inhibiting ALKBH5. Li *et al* (170) found that the ALKBH5-specific inhibitor ALK-04 inhibited melanoma growth and enhanced the response of melanoma to tumour immunotherapy.

Fang *et al* (174) identified an effective ALKBH5 inhibitor, 5-hydroxy-1-[4-((N-methylsulfamoyl)methyl)phenyl]-1H-pyrazole-3-carboxylic acid (20m), and the IC_{50} value was 0.021 μM in a fluorescence polarization assay. 20m is an effective, highly selective and cell-permeable inhibitor of ALKBH5, and could be used to explore further biological functions of ALKBH5 (174). The α-KG oxygenase inhibitors N-oxalylglycine (NOG) (IC_{50}, 25.85 μM) and pyridine dicarboxylic acid (PDCA; IC_{50}, 347.2 μM) are unreactive analogues of α-KG, whereas citrate (IC_{50}, 627.9 μM) and succinate (IC_{50}, 30 μM) are products of α-KG decarboxylation (40). The aforementioned four inhibitors, NOG, PDCA, succinate and citrate, are all located in the 2OG active site of ALKBH5 and chelated with Mn^{2+} (40,175). Selberg *et al* (169) identified two ALKBH5 inhibitors, 2-[(1-hydroxy-2-oxo-2-phenylethyl)sulfanyl]acetic acid (3) (IC_{50}, 0.84 μM) and 4-{[(furan-2-yl)methyl]amino}-1,2-diazinane-3,6-dione (6) (IC_{50}, 1.79 μM), which inhibited the proliferative ability of leukemic cells at low micromolar concentrations.

In addition, several research groups have identified ALKBH5 inhibitors that are not 2OG analogues (176,177). 8539-0746 has moderate ALKBH5 demethylase inhibitory activity, while 4-(Trifluoromethyl)benzyl 4-(6-(2,6-dihydroxy-3-nitrobenzoyl)pyrazolo[1,5-a]pyrimidin-2-yl)benzoate (DDO-2728) (IC_{50}, 2.97 μM) is an optimized inhibitor based on 8539-0746, as a novel and highly selective inhibitor of ALKBH5 with a 2OG-independent mechanism, selectively inhibiting the demethylase activity of ALKBH5 but not FTO (176). DDO-2728 targets the ALKBH5-transforming acidic coiled-coil containing protein 3 axis to induce the apoptosis and cell cycle arrest of AML cells, thereby inhibiting tumour progression (176). Komal *et al* (177) found that two ZINC15 compounds (ZINC78774792 and ZINC00546946), which bind to the ALKBH5 active site with the lowest binding energy, are potential ALKBH5 inhibitors that might have therapeutic value in the context of heart failure.

5. Conclusions, limitations and outlook

Increasing evidence has shown that epigenetic regulation serves a role in cancer. m^6A modification is the most vital and prevalent type of modification in human eukaryotic mRNAs. m^6A modification and its regulatory factors are closely associated with tumorigenesis and the development of tumours. With an increasing number of studies on m^6A, the m^6A demethylase ALKBH5 has received increasing attention. Previous studies on ALKBH5 have focused on its role in lung cancer, GBM and malignant haematological diseases (59,64,68,178-180), and emerging studies have shown that ALKBH5 is also extensively involved in various organic processes in digestive tract malignancies (67,75,84,91,109).

The current review indicates that the expression pattern and function of ALKBH5 in gastrointestinal tract cancer are controversial and that ALKBH5 has dual regulatory effects. ALKBH5 mainly serves as a cancer suppressor in OC, CRC, GBC and PC, suppresses the proliferation, migration and invasion of tumour cells, and regulates tumorigenesis, tumour progression, tumour metastasis, tumour drug resistance, tumour immunity and tumour metabolism. In GC, ICC and HBV-HCC, it functions as an oncogene and promotes

tumour development. However, some studies have reported the opposite results. But in HCC, ALKBH5 is dually regulated in HCC, and the number of studies on inhibiting and promoting the development of HCC is about the same. For example, in HCC, ALKBH5 inhibits the malignant biological properties of HCC, and low ALKBH5 expression is related to an unfavourable prognosis. ALKBH5 can also promote the proliferation, migration and invasion of HCC cells through the ALKBH5-MAP3K8 axis (73,88). Mechanistically, the role of ALKBH5 in gastrointestinal tract cancer is also complex, and ALKBH5 is associated with multiple target genes and molecular mechanisms through its m^{6}A methylation eraser function. For example, it is involved in the regulation of non-coding RNAs (ncRNAs), the coregulation of multiple m^{6}A readers and the maintenance of the stemness of tumour stem cells.

Given the functional importance of ALKBH5 as an independent prognostic marker for a variety of digestive tract tumours, there is great potential for the clinical application of ALKBH5 as a novel treatment target for digestive malignancies. Considering the different roles of ALKBH5 in different digestive system tumours, the therapeutic strategies of ALKBH5 in different tumour function will be discussed separately. One is as an oncogenic factor that is often highly expressed in cancer. One study has mentioned that vesicle-encapsulated ALKBH5 siRNA can be used in combination with anti-PD-1 treatment and can improve the efficacy of immunotherapy in CRC (61). To the best of our knowledge, inhibitors of ALKBH5 have only been studied in GBM, melanoma and hematologic tumours, but have not been observed in digestive system tumours. Further research on ALKBH5 inhibitors is expected in the future to achieve more efficient treatment. The other is as a tumour suppressor that is often downregulated in cancer. It has been mentioned in the literature that it is possible to treat tumours using nanomaterials with ALKBH5 mRNA to enhance ectopic ALKBH5 expression (86). Some tumours with low expression of ALKBH5 can be suitably treated with an ALKBH5 agonist to improve the antitumour efficacy (181); however, no studies on ALKBH5 agonists have been mentioned. Further research investigating ALKBH5 agonists should be conducted in the future.

Although numerous studies have revealed the function and mechanism of ALKBH5 in digestive system tumours, there are still some problems to be explored. First, as a potential biomarker for the clinical diagnosis, prognosis and treatment of digestive system tumours, the research investigating ALKBH5 in digestive system tumours is limited to clinical samples, bioinformatics data and animal models. Large-scale, multicenter, prospective clinical studies are needed to further improve the accuracy and specificity of ALKBH5 as a biomarker in digestive tumours. Second, there are still some unclear mechanisms of ALKBH5 regulating digestive system tumours, such as the regulation of ALKBH5 and ncRNAs, the function of ALKBH5 in cancer stem cells, and the role of ALKBH5 in GBC. Some studies have only focused on the role of ALKBH5 in altering the RNA levels of downstream genes but have not addressed whether ALKBH5 regulates downstream genes by remodelling downstream structures, altering the stability of downstream transcripts or acting as ceRNAs. ALKBH5 is related to the maintenance of stemness of cancer stem cells and is involved in tumour progression and tumour drug resistance; however, there are few studies on ALKBH5 in cancer stem cells. In GBC, few studies have been conducted on ALKBH5, and further studies should examine the function of ALKBH5 in GBC. Third, although ALKBH5 has been shown to be a promising therapeutic target, at present, inhibitors of ALKBH5 have only been studied in animal experiments in some tumours and lack clinical practice. In addition, agonists targeting ALKBH5 as well as liposomes and nanomaterials loaded with ALKBH5 drugs also need to be further developed.

In conclusion, the expression, function and regulatory mechanisms of ALKBH5 in gastrointestinal tumours are summarized, suggesting that ALKBH5 serves a key role in the tumorigenesis and progression of gastrointestinal tumours. This means that ALKBH5 is a potential diagnostic, prognostic and therapeutic biomarker in digestive tract tumours. However, there are still some problems to be explored. The research of ALKBH5 lacks large-scale clinical data to verify the accuracy and specificity of ALKBH5 as a biomarker, the specific regulatory mechanism of ALKBH5 still needs further elucidation, and the specific targeted drug development of ALKBH5 is insufficient and clinical practice is lacking. More large-scale, multicenter data and prospective clinical studies are required in the future to further validate the accuracy of ALKBH5 as a biomarker and promote the application of personalized medicine for gastrointestinal cancer in clinical practice.

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Authors' contributions

LZ and MJ designed and wrote the original draft. QS and XY acquired the data. LZ, MJ, YO, YP, WY and YF edited and revised the manuscript. All authors read and approved the final version of the manuscript and agreed to accountable for all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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