Table SI. Roles of ALKBH5 in human gastrointestinal tract cancers.

A, Oesophageal cancer								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Xiao *et al*, 2021	Downregulated	Tumour suppressor	-	-	-	-	Suppresses cell proliferation, migration and invasion	(91)
Chen *et al*, 2021	Downregulated	Tumour suppressor	-	Pri-miR-194-2	ALKBH5-miR-194-2-RAI1-Hippo pathway	-	Suppresses cell proliferation, migration and invasion	(92)
Xue *et al*, 2021	Downregulated	Tumour suppressor	miR-193a-3p↑	Pri-miR-193-3p	miR-193-3p-ALKBH5 positive feedback loop	-	Suppresses cell proliferation, migration and invasion	(93)
Qiao *et al*, 2023	Upregulated	Tumour suppressor	SHMT2↑	C-myc↑	SHMT2-METTL3-FTO/ALKBH5-c-myc-IGF2BP2 pathway	IGF2BP2	-	(94)
Nagaki *et al*, 2020	Upregulated	Oncogene	-	CDKN1A (p21)↓	ALKBH5-CDKN1A axis	-	Promotes cell proliferation and migration, and accelerates cell cycle progression	(95)
Wu *et al*, 2022	Upregulated	Oncogene	-	lncRNA CASC8↑	ALKBH5-CASC8-hnRNPL-Bcl2/caspase3 pathway	-	Promotes cell proliferation	(96)
B, Gastric cancer								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Zhang *et al*, 2019	Upregulated	Oncogene	-	lncRNA NEAT1↑	ALKBH5-lncRNA NEAT1-EZH2 pathway	-	Promotes cell invasion and migration	(84)

Wang *et al*, 2021	-	Oncogene	lncRNA NRON↑	Nanog↑	lncRNA NRON-ALKBH5-Nanog pathway	-	Promotes cell proliferation	(85)
Fang *et al*, 2022	Upregulated	Oncogene	-	lncRNA TP53TG1↓	ALKBH5-lncRNA TP53TG1-CIP2A-PI3K/AKT pathway	-	-	(104)
Fang *et al*, 2023	Upregulated	Oncogene	LINC00659↑	JAK1↑	LINC00659-ALKBH5-JAK1/STAT3-YTHDF2 pathway	YTHDF2	Promotes cell proliferation, migration and invasion	(74)
Chen *et al*, 2023	Upregulated	Oncogene	-	CHAC1↓	ALKBH5-CHAC1-ROS pathway	-	Promotes cell proliferation, migration and invasion	(78)
Wang *et al*, 2024	Upregulated	Oncogene	-	ZKSCAN3↑	ALKBH5-ZKSCAN3-YTHDF2-VEGFA pathway	YTHDF2	Promotes cell migration and invasion	(102)
Wang *et al*, 2024	Upregulated	Oncogene	-	circFOXP1↑	ALKBH5-circFOXP1-miR-338-3p-SOX4 pathway	-	-	(105)
Suo *et al*, 2024	Upregulated	Oncogene	HSPA4↑	CD58↓	HSPA4-ALKBH5-CD58	-	Inhibits the infiltration of $CD8^+$ T cells	(106)
Ji *et al*, 2023	Downregulated	Tumour suppressor	-	SLC7A2, CGB3↓	ALKBH5-SLC7A2/CGB3 axis	-	-	(101)
Hu *et al*, 2022	Downregulated	Tumour suppressor	-	PKMYT1↑	ALKBH5-PKMYT1-IGF2BP3 pathway	IGF2BP3	Suppresses cell invasion and migration	(70)
Wang *et al*, 2023	Downregulated	Tumour suppressor	-	YY1↑	ALKBH5-YY1-YTHDF1-ATG4B pathway	YTHDF1	Suppresses cell proliferation, migration and invasion	(107)
C, Colorectal cancer								
First author/s,	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)

year								
Zhang *et al*, 2022	Downregulated	Tumour suppressor	-	PHF20↑	ALKBH5-PHF20 axis	-	Suppresses cell proliferation, migration and invasion	(109)
Luo *et al*, 2023	Downregulated	Tumour suppressor	-	SLC7A11↑	ALKBH5-SLC7A11 axis	-	Suppresses cell proliferation and promotes cell ferroptosis	(110)
Ge *et al*, 2023	Downregulated	Tumour suppressor	-	CCL5↑	ALKBH5-NF-κB-CCL5 pathway	-	Suppresses cell proliferation, migration and invasion	(113)
Wu *et al*, 2021	Downregulated	Tumour suppressor	-	FOXO3↓	ALKBH5-FOXO3- miR-21-SPRY2 pathway	-	Suppresses cell proliferation, migration and invasion	(114)
Wu *et al*, 2023	Downregulated	Tumour suppressor	HDAC2↑	JMJD8↑	METTL14/ALKBH5-JMJD8-IGF2BPs-PKM2 pathway	IGF2BPs	Suppresses cell proliferation	(86)
Ye *et al*, 2023	Downregulated	Tumour suppressor	-	HK2↑	FTO/ALKBH5-HK2-IGF2BP2-FOXO1 pathway	IGF2BP2	Suppresses cell proliferation, migration and invasion	(116)
Ye *et al*, 2023	Downregulated	Tumour suppressor	-	FABP5↓	ALKBH5-FABP5-FASN-mTOR pathway	-	Suppresses cell proliferation, migration and invasion	(87)
Liu *et al*, 2024	Downregulated	Tumour suppressor	p53	lncRNA CARMN↓	p53-ALKBH5-lncRNA CARMN-YTHDF2/YTHDF3-miR-5683-FGF2-Akt/mTOR pathway	YTHDF2/YTHDF3	Suppresses cell proliferation and migration	(118)
Feng *et al*, 2024	Downregulated	Tumour suppressor	-	Arg-1↑	ALKBH5-Arg-1 axis	-	Suppresses the progression of CRC by affecting the immunosuppressive function of MDSCs	(119)
Shao *et al*,	Upregulated	-	-	CircAFF2↑	ALKBH5-circAFF2-	YTHDF2	Increases the radiosensitivity of CRC	(117)

2023					YTHDF2-CAND1-Cullin1/NEDD8 pathway		cells	
Zhai *et al*, 2023	Upregulated	Oncogene	-	AXIN2↓	ALKBH5-AXIN2-IGF2BP1-Wnt/β-catenin-DKK1 pathway	IGF2BP1	Promotes cell proliferation	(61)
Shen *et al*, 2023	Upregulated	Oncogene	-	RAB5A↑	ALKBH5-RAB5A-YTHDF2 pathway	YTHDF2	Promotes cell proliferation, migration and invasion	(69)
Guo *et al*, 2020	Upregulated	Oncogene	-	lncRNA NEAT1↑	ALKBH5-lncRNA NEAT1 axis	-	Promotes cell proliferation and migration, and suppresses cell apoptosis	(120)
Sun *et al*, 2024	Upregulated	Oncogene	-	CPT1A↑	ALKBH5-CPT1A axis	-	Promotes cell proliferation, migration and invasion	(127)
Li *et al*, 2023	Upregulated	Oncogene	miR-140-3p	BET1L↑	Rs11245997-miR-140-3p-METTL14/WTAP/ALKBH5-BET1L-HSD17B7/CYP27B1/COMT pathway	-	-	(128)
D, Hepatocellular carcinoma								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Chen *et al*, 2020	Downregulated	Tumour suppressor	-	LYPD1↑	ALKBH5-LYPD1-IGF2BP1 pathway	IGF2BP1	Suppresses cell proliferation, migration and invasion	(67)
Wang *et al*, 2023	Downregulated	Tumour suppressor	-	PAQR4↑	ALKBH5-PAQR4-IGF2BP1-PI3K/AKT	IGF2BP1	Suppresses cell proliferation, migration and invasion	(73)

					pathway			
Zhang *et al*, 2022	Downregulated	Tumour suppressor	-	lncRNA LINC02551 ↑	ALKBH5-lncRNA LINC02551-DDX24 pathway	IGF2BP1	-	(131)
Wang *et al*, 2022	Downregulated (non-alcoholic fatty liver disease-HCC)	Tumour suppressor	-	lncRNA LINC01468 ↑	ALKBH5-lncRNA LINC01468-SHIP2-PI3K/AKT/mTOR pathway	-	-	(133)
Zhao *et al*, 2022	Downregulated	Tumour suppressor	-	UBR7↓	ALKBH5-UBR7-Keap1-Nrf2-Bach1-HK2 pathway	-	-	(134)
You *et al*, 2022	Upregulated	Oncogene	-	MAP3K8↑	ALKBH5-MAP3K8-YTHDF2-JNK/ERK pathway	YTHDF2	Promotes cell proliferation, migration and invasion	(88)
Chang *et al*, 2024	Upregulated	Oncogene	-	TTI1↑	ALKBH5-TTI1 axis	-	Promotes cell proliferation, migration and invasion	(130)
Liu *et al*, 2020	-	Oncogene	CircRNA cIARS↑	-	CircRNA cIARS-ALKBH5 axis	-	Suppresses cell ferroptosis and autophagy under sorafenib treatment	(135)
Adjibade *et al*, 2024	-	-	-	ATF4↑	ALKBH5/FTO-ATF4 axis	-	Promotes resistance to sorafenib treatment of HCC cells	(136)
Yeermaike *et al*, 2022	Upregulated	Oncogene	-	lncRNA NEAT1↑	ALKBH5-lncRNA NEAT1-miR-214-PSMB8 pathway	-	Promotes cell migration	(137)
Chen *et al*, 2021	Upregulated	Oncogene	lncRNA CASC11↑	UBE2T↑	lncRNA CASC11-ALKBH5-UBE2T-YTHDF2 pathway	YTHDF2	-	(80)
Liu *et al*,	-	Oncogene	-	Circ-CCT3↑	ALKBH5/METTL3-circ-	YTHDF2	-	(138)

2023					CCT3-YTHDF2-miR-378a-3p-FLT-1 pathway			
Chen *et al*, 2022	Upregulated	Oncogene	-	CircCPSF6↑	ALKBH5-circCPSF6-YTHDF2-YAP1 pathway	YTHDF2	-	(139)
Meng *et al*, 2024	Upregulated (HBV-HCC)	Oncogene	-	SNAI2↑	ALKBH5-SNAI2-YTHDF2 pathway	YTHDF2	Promotes stemness maintenance and self-renewal in HBV-positive HCC	(141)
Qu *et al*, 2021	Upregulated (HBV-HCC)	Oncogene	WDR5↑	HBx↑	HBx-WDR5-ALKBH5 positive feedback loop	-	Promotes cell proliferation and migration	(143)
E, Intrahepatic cholangiocarcinoma								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Gao *et al*, 2024	Upregulated	Oncogene	-	BUB1B↑	ALKBH5-BUB1B axis	-	Promotes cell proliferation and stemness maintenance	(145)
Qiu *et al*, 2021	Upregulated	Oncogene	-	PD-L1↑	ALKBH5-PD-L1-YTHDF2 pathway	YTHDF2	Inhibits T-cell-mediated antitumour immunity	(146)
F, Gallbladder cancer								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Wu *et al*, 2024	Downregulated	Tumour suppressor	TGF-β1↑	FOXA1↓	TGF-β1-ALKBH5-FOXA1 pathway	-	-	(149)
G, Pancreatic cancer								
First author/s,	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)

year								
Tang *et al*, 2020	Downregulated	Tumour suppressor	-	WIF-1↑	ALKBH-WIF-1-Wnt pathway	-	Suppresses cell proliferation, migration and invasion, and improves the sensitivity to chemotherapy	(75)
Lin *et al*, 2022	Downregulated	Tumour suppressor	-	lncRNA SH3BP5-AS1↑	ALKBH5-lncRNA SH3BP5-AS1-IGF2BP1-miR-139-5p-CTBP1-Wnt/β-catenin pathway	IGF2BP1	-	(89)
Zhang *et al*, 2022	Downregulated	Tumour suppressor	-	lncRNA DDIT4-AS1↑	ALKBH5-lncRNA DDIT4-AS1-UPF1-DDIT4-mTOR pathway	-	-	(77)
Guo *et al*, 2020	Downregulated	Tumour suppressor	-	PER1↓	ALKBH5-PER1-YTHDF2-ATM-P53-ALKBH5 loop	YTHDF2	Suppresses cell proliferation, migration and invasion	(79)
He *et al*, 2018	Downregulated	Tumour suppressor	-	lncRNA KCNK15-AS1↓	ALKBH5-lncRNA KCNK15-AS1 axis	-	Suppresses cell migration and invasion	(154)
He *et al*, 2021	Downregulated	Tumour suppressor	-	lncRNA KCNK15-AS1↓	ALKBH5-lncRNA KCNK15-AS1-KCNK15/PTEN-AKT pathway	-	-	(90)
Lai *et al*, 2022	Downregulated	Tumour suppressor	-	CELF2↓	ALKBH5-CELF2-YTHDF2-CD44-ERAD pathway	YTHDF2	-	(155)
Huang *et*	Downregulated	Tumour	-	FBXL5↓	ALKBH5-FBXL5-	-	Suppresses cell migration and	(156)

al, 2021		suppressor			IRP2/SNAI1 pathway		invasion	
Liu *et al*, 2023	Upregulated (hypoxia)	Oncogene	HIF1α↑	HDAC4↑	ALKBH5-HDAC4-YTHDF2-HIF1α positive feedback loop	YTHDF2	Promotes cell proliferation and migration	(72)
H, Pancreatic neuroendocrine tumours								
First author/s, year	Expression	Role in cancer	Upstream	Target	Mechanism	Readers	Biological function	(Refs.)
Chen *et al*, 2023	Upregulated	Oncogene	-	FABP5↑	ALKBH5-FABP5-IGF2BP2-PI3K/AKT/mTOR pathway	IGF2BP2	Promotes cell proliferation, migration and invasion	(159)

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ALKBH5, AlkB homologue 5; lncRNA, long non-coding RNA; miR, microRNA; LINC, long-integrated non-coding; ERAD, endoplasmic reticulum-associated degradation; circRNA/circ, circular RNA; CRC, colorectal cancer; MDSC, myeloid-derived suppressor cell; ROS, reactive oxygen species.

Table SII. Small-molecule inhibitors of AlkB homologue 5.

First author/s, year	Inhibitor	Identification method	PDB code	IC_{50} (method, substrate)	Anticancer potency (cell lines)	(Refs.)
Takahashi *et al*, 2022	Ena15	Virtual screening	4NRO	18.3±1.8 μM (ELISA, ssDNA)	Inhibits tumour growth and induces cell cycle arrest in GBM (LN229, KNS81, U87MG and U251MG cells)	(168)
	Ena21	Virtual screening	4NRO	15.7±1.0 μM (ELISA, ssDNA)	Inhibits tumour growth and induces cell cycle arrest in GBM (LN229, KNS81, U87MG and U251MG cells)	
Malacrida *et al*, 2020	MV1035	-	4OCT	-	Inhibits cell migration and invasiveness of GBM (U87 cells)	(171)
Li *et al*, 2016; Tang *et al*, 2022	IOX1	-	-	2.9±0.3 μM (Top-Count NXT HTS, ^{3}H-m^{6}A-ssRNA)	Slows tumour growth rate of GBM (U87 cells)	(172,173)
Li *et al*, 2020	ALK-04	Virtual screening	4NRO	-	Inhibits tumour growth of melanoma (B16 cells)	(170)
Fang *et al*, 2022	20m	Virtual screening; molecular docking	4NRQ	0.021 μM (FP, ssRNA)	-	(174)
Feng *et al*, 2014	2,4-PDCA	Structural similarity screening	4NRQ	347.2 μM (HPLC, ssDNA)	-	(40)
	Citrate	Structural similarity screening	4O61	627.9 μM (HPLC, ssDNA)	-	
	NOG	Structural similarity screening	4NRP	25.85 μM (HPLC, ssDNA)	-	
	Succinate	Structural similarity screening	4NPM	30.00 μM (HPLC, ssDNA)	-	

Selberg *et al*, 2021	2-[(1-hydroxy-2-oxo-2-phenylethyl) sulfanyl] acetic acid (3)	Virtual screening; molecular docking	4O61	0.84 μM (ELISA, RNA)	Inhibits tumour growth of AML (HL-60, CCRF-CEM and K562 cells)	(169)
	4-[((furan-2-yl) methyl) amino]-1,2-diazinane-3,6-dione (6)	Virtual screening; molecular docking	4O61	1.79 μM (ELISA, RNA)	Inhibits tumour growth of AML (HL-60, CCRF-CEM and K562 cells)	
Wang *et al*, 2023	8539-0746	Virtual screening	4NRO	15.6 μM (FP, ssDNA)	-	(176)
	DDO-2728	Virtual screening; optimization; molecular docking	4NRO	2.97 μM (FP, ssDNA)	Induces cell apoptosis, induced cell cycle arrest and inhibits tumour growth of AML (MOLM-13 and MV4-11 cells)	
Komal *et al*, 2023	ZINC78774792	Virtual screening; molecular docking	4NJ4	-	-	(177)
	ZINC00546946	Virtual screening; molecular docking	4NJ4	-	-	

FP, fluorescence polarization; HPLC, high-performance liquid chromatography; GBM, glioblastoma; AML, acute myeloid leukaemia; ssDNA, single-stranded DNA; ssRNA, single-stranded RNA; HTS, high-throughput screening; 20m, 5-hydroxy-1-[4-((N-methylsulfamoyl)methyl)phenyl]-1H-pyrazole-3-carboxylic acid; PDCA, pyridine dicarboxylic acid; ^{3}H-m^{6}A-ssRNA, 3H-monomethylated ss-RNA; ALK-04; DDO-2728, 4-(Trifluoromethyl)benzyl 4-(6-(2,6-dihydroxy-3-nitrobenzoyl)pyrazolo[1,5-a]pyrimidin-2-yl)benzoate; Ena15; Ena21; IOX1, 5-carboxy-8-hydroxyquinoline; MV1035, 2-methyl-3-propyl-5H-imidazo[1,2-c][1,3]benzoxazin-5-thione; NOG, N-oxalylglycine; NXT; PDB, Protein Data Bank; ZINC00546946; ZINC78774792.