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Review

A review on the role of ncRNAs in the pathogenesis of cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma is a rare tumor but a challenging cancer in terms of pathological changes, clinical manifestations and therapeutic options. Recent studies have provided evidence for participation of non-coding RNAs in the carcinogenic process of cholangiocarcinoma. We demonstrate the role of long non-coding RNAs, microRNAs and circular RNAs in the pathogenesis of cholangiocarcinoma and highlight their significant position as therapeutic targets and biomarkers for this type of cancer. We also list a number of molecular axes comprising these non-coding RNAs that represent potential targets for therapeutic options in cholangiocarcinoma, based on their significant roles in the regulation of cell proliferation, differentiation and apoptosis of these cells.

1. Introduction

Cholangiocarcinoma is a rare tumor covering around 3 % of gastrointestinal tumors. This cancer has a global incidence rate of less than 2 in 100,000 [1]. Intrahepatic cholangiocarcinoma is a primary cancer being associated with major challenges in terms of pathological changes, clinical manifestations and therapeutic options. Typically, it originates from malignantly transformed cholangiocytes neighboring the small portal bile duct to second-order segmental large bile ducts. From a macroscopic point of view, it has three main growth pattern, namely mass-forming, periductal infiltrative and intraductal growth [2]. Mass-forming is the most common type, comprising about two third of all cases [3,4].

Histologically, intrahepatic cholangiocarcinomas are most typically adenocarcinomas with biliary differentiation originated from intrahepatic biliary tree [2]. This type of cancer is evolved through a multistep process initiating from a flat intraepithelial biliary neoplastic lesion and evolving into intraductal papillary neoplasm of the bile duct and intraductal tubulo-papillary neoplasm, respectively [2].

Recent studies have provided evidence for participation of non-coding RNAs in the carcinogenic process of cholangiocarcinoma. These transcripts encompass a wide array of regulatory and non-regulatory transcripts. The former types of transcripts are the main focus of the current review. In fact, we demonstrate the role of long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) in the pathogenesis of cholangiocarcinoma and highlight their significant position as therapeutic targets and biomarkers for this type of cancer.

2. Up-regulated lncRNAs

LncRNAs can regulate expression of genes at different levels [5]. These transcripts have sizes more than 200 nt and influence several aspects of tumorigenesis, such as cell proliferation and differentiation, apoptotic pathways, cell cycle transition, invasive properties, metastatic ability and DNA damage response. Several lncRNAs have been found to be up-regulated in cholangiocarcinoma acting as tumor promoters (Table 1, Fig. 1). Most of these lncRNAs have been found to affect carcinogenic processes in other cancers as well [6–8]. For instance, expression of CCAT1 has been found to be significantly increased in

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Table 1
Up-regulated lncRNAs in cholangiocarcinoma.

LncRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
AFAP1-AS1	HuCCT1, TFK-1, HIBEpic	–	–	AFAP1-AS1 is linked to CCA growth. AFAP1-AS1 has the ability to be a treatment option for CCA.	[12]
CCAT1	–	–	–	CCAT1 is linked to aggressive and malignant tendencies.	[9]
NEAT1	HuCCT1, RBE, HCCC-9810, HCCCT-1, HIBEC	PI3K/AKT	miR-186-5p/ PTP4A1	CCA cell growth is aided by NEAT1. NEAT1 might be a feasible treatment option for CCA.	[10]
MALAT1	HIBEpiC, RBE, HUH28, FRH0201, QBC939, SNU-1196	–	miR-204/CXCR	MALAT1 level in HCCA tissues is inversely linked with survival times.	[11]
CPS1-IT1	L-02, Huh-7, Bel-7402, ICC-9810, HepG2, MHCC-97 L	–	–	CPS1-IT1 boosts growth of ICC cells. CPS1-IT1 might be a possible biomarker and prediction indicator.	[13]
TM4SF1-AS1	–	–	miR-744-3p	TM4SF1-AS1 has been discovered as a CCA prediction indicator. By regulating miR-744-3p, TM4SF1-AS1 acted as a tumor promoter for CCA.	[14]
GIHCG	–	–	–	Expression of GIHCG is relevant to patient survival. It is predicted to become a novel molecular marker for CCA treatment.	[15]
LINC00630	HuCCT1, RBE, CCLP-1, HCCC-9810, HIBEC	–	miR-199a/ FGF7	LINC00630 may be an oncogenic lncRNA that promotes tumor growth.	[16]
TMPO-AS1	HCCC-9810, HuCCT1, RBE, HIBEC	–	Let-7 g-5p/ HMGA1	TMPO-AS1 increases cell growth in CCA cells, while inhibiting cell death.	[17]
PSMA3-AS1	CCLP-1, QBC939	–	miR-3761-3p/ LAMC1	PSMA3-AS1 is a novel lncRNA for tumor growth.	[18]
CHRM3.AS2 MIR205HG LINC00661	–	Autophagy	–	A profile of three lncRNAs with predictive significance for CCA has been discovered by an arlncRNA coexpression network.	[19]
TUG1	RBE, QBC939, HuH28, HIBEC	–	miR-29a	Through the modulation of miR-29a expression, TUG1 enhances growth of CCA cells.	[20]
AGAP2-AS1 AP005233.2	–	Nicotinate and nicotinamide metabolism Butanoate metabolism Regulation of autophagy Pantothenate and COA biosynthesis	–	This signature confidently predicted clinical outcome in patients with ICCA. This is closely associated with metabolic pathways.	[21]
PCAT6	ICC-9010	–	miR-330-5p	PCAT6 aberrant expression leads to ICC cell growth via influencing miR-330-5p.	[22]
SNHG16	RBE, HuCCT1	–	miR-146a-5p/ GATA6	By modulating the miR-146a-5p/GATA6 axis, SNHG16 increases cell proliferation while suppressing apoptosis.	[23]
Lnc-ATB	HuCCT1, RBE, TFK1, Huh-28	–	miR-200c/ PCNA	In vivo decreasing lnc-ATB enhanced miR-200c signals, which reduced tumor formation and decreased PCNA expression in tumor tissues.	[24]
HOTAIR	HuB28, HuCCT1	–	miR-204-5p/ HMGB1	LncRNA HOTAIR controls HMGB1 to reduce cell death and stimulate cell growth.	[25]
RHPN1-AS1	RBE, TFK1, HCCC9810, QBC939, HuCCT1, HiBEC	–	miR-345-5p/ YAP1	RHPN1-AS1 may be a useful biomarker for assessing prognosis in CCA and might lead to novel CCA therapeutic methods.	[26]
DANCR	–	–	miR-345-5p/ Twist1	DANCR influenced cell growth and caused cell death through altering miR-345-5p.	[27]
SNHG1	HCCC-9810, SSP25, RBE, HuCCT1, HIBEC	NF-κB	miR-140/TLR4	SNHG1aids CCA carcinogenesis. SNHG1 could be used as a targeted therapy for CCA.	[28]
ST8SIA6-AS1	TFK-1, CCLP, RBE, HuCCT1, HIBEC	–	miR-145-5p/ MAL2	ST8SIA6-AS1 may aid CCA cells growth and migration.	[29]
FLVCR1-AS1	RBE, HCCC-9810, HuCCT1, CCLP1, HIBEC	–	miR-485-5p	In CCA, FLVCR1-AS1 has been shown to behave as an oncogene. It might be a new diagnostic marker and a treatment option.	[30]
ASAP1-IT1	KMBC, HuH-28, QBC939, HuCCT1, CCLP1, RBE	Hedgehog	–	ASAP1-IT1 served as a tumor motivator and altered the hedgehog signal pathway.	[31]
FAM66C	HuCCT1, TFK-1, CCLP-1, QBC939, RBE	–	miR-23b-3p/ KCND2	In the ICC, FAM66C enhanced cell survival.	[32]
SNHG12	BEC, CCLP-1, TFK-1, HuCCT1, RBE	–	miR-199a-50/ Klotho	SNHG12 aided ICC cell growth and invasion.	[33]
LINC00184	KMBC, HuCCT1, QBC939, HIBEC	–	miR-23b-3p/ ANXA2	LINC00184 enhanced CCA cell growth.	[34]
GAS5	RBE, CCLP1, HuCCT1, HCCC-9810, HIBEC	–	miR-1297	Through its regulating of miR-1297, GAS5 aided CCA growth.	[35]
FOXD2-AS1	CCLP-1, QBC939, HuCCT1, RBE	–	miR-760/E2F3	Elevation of FOXD2-AS1 is a poor predictive sign.	[36]
LINC00665		Wnt/β-catenin	miR-424-5p/ BCL9L		[37]

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
	HuCCT1, HuH28, SNU-1196, SNU-1079, SNU308, SNU-245, SNU-478, SNU-869, HEK293T			Suppressing LINC00665 reduced gemcitabine endurance in CCA patients, whereas elevation of this lncRNA indicated bad prognosis.	
DLGAP1-AS2	HuCCT1, RBE, HEBEpics	–	miR505/ GALNT10	The DLGAP1-AS2/miR-505/GALNT10 axis may have a role in controlling CCA malignant growth.	[38]
MNX1-AS1	RBE, QBC939, FRH0201, HIBEpiC, HUVECs	Hippo signaling pathway	Ajuba - cMyc	MNX1-AS1 can promote cancer development through the MNX1-AS1/c-Myc and MAZ/MNX1/Ajuba/hippo pathways.	[39]
LINC00667	CCLP1, RBE, QBC939, HCCC-9810	–	miR-200c-3p/ PDK1	The YY1/LINC00667/miR-200c-3p/PDK1 axis might be used to develop a novel CCA therapy approach.	[40]
CASC15	CCLP, RBE, 9810, HuCCT1	PI3K/AKT	PRDX2 and Ki67	CASC15 is thought to increase ICC cell motility, invasion, proliferation and tumor development while inhibiting ICC cell death.	[41]
SNHG20	RBE, QBC939, CCLP-1, TFK-1	–	miR-520f-3p	CCA proliferation is strongly linked to overexpressed SNHG20 and might be inhibited by knocking down SNHG20 expression.	[42]
LINC00473	HCCC-9810, CCLP1, RBE, QBC939, HuCCT1, KMBC, HIBEC	–	miR-506/DDX5	LINC00473 was shown to perform an oncogenic effect in CCA development.	[43]
LINC00261	CCLP1, RBE, QBC939, HuCCT1, Huh-28, HIBEC	–	–	Increased level of linc00261 in CCA implies a poor prognosis and facilitates metastasis.	[44]
ZFAS1	CCLP1, RBE, QBC939, HuCCT1	–	miR-296-5p/ USF1	ZFAS1 overexpression forecasts a dismal prognosis for CA and boosts proliferation.	[45]
PCAT1	CCLP1, RBE, QBC939, HCCC-9810, HIBEC	–	miR-216a-3p BCL3	In CCA, PCAT1 is a new carcinogenic molecule. Its up-regulation suggested a bad prognosis.	[46]
Sox2ot	RBE, QBC939, HIBEC	–	–	Overexpression of Sox2ot is linked to lymph node invasion and postoperative recurrence.	[47]
SNHG3	–	–	miR-3173-5p/ ERG	In CCA, SNHG3 is a pleiotropic carcinogenic lncRNA in CCA cells.	[48]
HOTTIP	QBC939, CCLP-1	–	miR-637/ LASP1	Increased amount of HOTTIP is linked to chemo-responsiveness. Under presence of gemcitabine and cisplatin HOTTIP influenced growth of cancerous cells.	[49]
AGAP2-AS1	RBE, HuCCT1, HIBEpic	–	CDKN1A	AGAP2-AS1 activation is attributed to a worse prognosis in CCA. By reducing CDKN1A production, AGAP2-AS1 increases CCA cell proliferation.	[50]
HOXD-AS1	CCLP1, RBE, QBC939, TFK-1, HIBEC	–	miR-520c-3p/ MYCN	Elevated HOXD-AS1 is strongly linked to poor CCA patient survival.	[51]
HOGLROS	QBC939, HuCCT1, HCCC-9810, KMCH	m-TOR	–	HAGLROS reduction improved lipid metabolism reprogramming in ICC.	[52]
ANRIL	HuCCT1, RBE	–	ERRFI1	ANRIL enhances CCA neoplasm by epigenetically controlling ERRFI1 production in the nucleus, making it easier for CCA cells to survive and spread.	[53]
ZEB1-AS1	HuH28, HuCCT1, RBE, CCLP-1, HCCC-9810	–	miR-200a/ZEB	ZEB1-AS1 upregulation increases IHCC development by hastening proliferation.	[54]
SNHG6	HCCC-9810, RBE, HIBEpiC	–	miR-101-3p/ E2F8	SNHG6 might be a feasible treatment option for CCA.	[55]
NNT-AS1	SG231, HuCCT1, CCLP1, TFK1, H69	PI3K/AKT – ERK1/2	miR-203	By decreasing the expression of miR-203, NNT-AS1 acted as an oncogene in CCA formation.	[56]
LINC01410	HuCCT1, CCLP1, HuH-28, QBC939, RBE	–	miR-124-3p/ SMAD5	CCA cell growth and migration are all reduced when LINC01410 is knocked down.	[57]
Lnc-LFAR1	QBC939	TGFb/Smad	–	Reduction of lnc-LFAR1 can alter the occurrence of CCA by suppressing cell growth through affecting the TGF/Smad pathway.	[58]
LINC01503	RBE, QBC939, HIBEC	–	–	LINC01503 is abundantly expressed in CCA and may actively stimulate cancer cell growth.	[59]
UCA1	RBE, HCCC-9810, LICCF, HIBEC	–	miR-122	The lncRNA UCA1 enhances ICC growth by limiting miR-122, implying that the UCA1/miR-22 connection might be utilized as a treatment option.	[60]
LOXL1-AS1	RBE, HuCCT1, Huh-28, CCLP1, HIBEC	–	miR-324-3p/ ABCA1	Cell growth might be aided by LOXL1-AS1 while cell death could be minimized in CCA.	[61]
LINC01061	Huh-28, HuCCT1, KKU-214, RBE, MMNK-1	–	miR-612/ SEMA4D	The production of LINC01061 is higher in CCA and knocking it down hindered cell growth, caused apoptosis and restricted cell migration.	[62]
PVT1	HuCCT1, RBE	–	ANGPTL4	PVT1 can increase CCA cancer by modulating ANGPTL4 transcription.	[63]
Lnc-EPIC1	KKU-055, KKU-100, KKU-213, KKU-214, MMNK-1	–	MYC	Lnc-EPIC1 boosts CCA tumorigenesis by targeting MYC. lnc-EPIC1 leads to CCA cell proliferation.	[64]
HOTAIR	HuCCT1, RBE, CCLP-1, Huh-28, QBC939, HIBEC	–	–	Elevated HOTAIR could be a bad prognostic factor.	[65]
SNHG1	HuCCT1, RBE	–	CDKN1A	SNHG1 may increase CCA malignancy by controlling CDKN1A production, allowing CCA cells to survive and spread.	[66]
TTN-AS1	RBE, HCCC9810, CC262, QBC939, FRH0201, HIBEC	TGF-β pathway	miR320a/ neuropilin-1	TTN-AS1 activation in CCA is attributed to clinical manifestations of the disease.	[67]
HEIH	RBE, TFK1, CCLP1, QBC939, HuCCT1, BEC	–	miR-98-5p/ HECTD4	By regulating the miR-98-5p/HECTD4 axis, HEIH accelerated CHOL carcinogenesis.	[68]
LINC01296	HIBEC, RBE, CCLP1, HuCCT1, HCCC-9810	–	miR-5095/ MYCN	Cell growth is linked to LINC01296.	[69]
PANDAR		–	–		[70]

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
	HCCC-9810, RBE, QBC939, Huh-28, HuCCT1, KMBC, CCLP-1, HIBEC			As a possible diagnostic marker and therapy option for the treatment of CCA cancer, PANDAR performs oncogenic functions in CCA.	
H19	RBE, HCCC-9810, QBC939, Huh-28, HuCCT1, KMBC, CCLP-1, HIBEC	–	–	H19 inhibition reduces the capacity for invasion.	[71]
CCAT2	HUH28, HuCCT1, RBE, HCCC9810, H69	–	–	CCAT2, may enable the development and spread of the disease.	[66]
TP73-AS1	HCCC-9810, RBE, QBC939, Huh-28, HuCCT1, KMBC, CCLP-1, HIBEC	–	–	The capacity of CCA cells to migrate can be facilitated by TP73-AS1.	[72]
SPRY4-IT1	RBE, HCCC-9810, HIBEC, CCLP-1, HuCCT1, Huh-28, KMBC, QBC939	–	EZH2, LSD1 and DNMT1	Human CCA cells have an elevated level of SPRY4-IT1.	[73]
CRNDE	HIBEpic, HuCCT1, RBE, HCCC9810, HUH28	–	–	The development of IHCC is linked with CRNDE production.	[74]
LMCD1-AS1	RBE, KMBC, QBC939, HCCC-9810, HuCCT1, HIBEC	–	miR-345e-5p/ COL6A3	The carcinogenesis of CCA requires the E2F1/LMCD1-AS1/miR-345e-5p/COL6A3 axis.	[75]

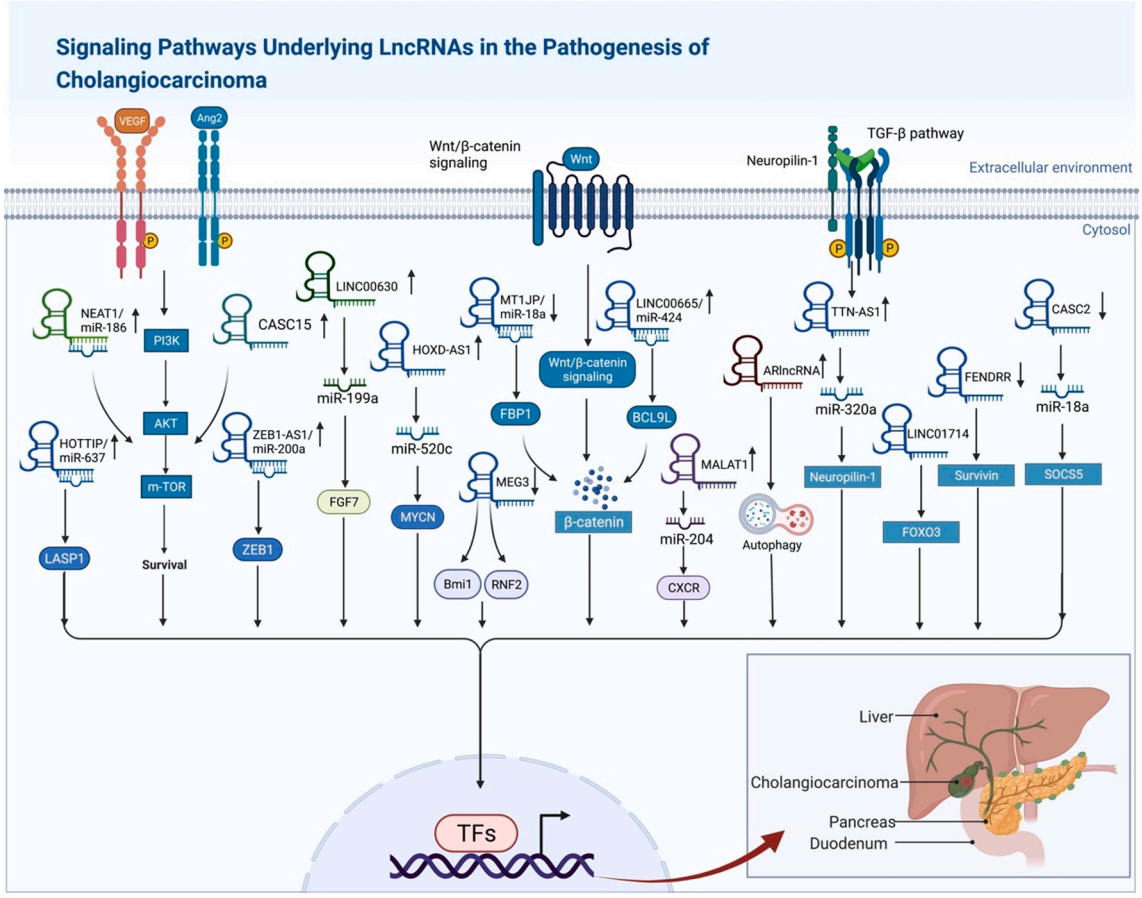

Fig. 1. The progression of cholangiocarcinoma is linked to the participation of a number of distinct signaling pathways, each of which is governed by lncRNAs.

cholangiocarcinoma tumor tissues compared with control tissues. Notably, expression of this oncogenic lncRNA has been associated with differentiation level of cancer cells, their invasion to regional lymph nodes and TNM stage. Moreover, over-expression of CCAT1 has been shown to predict poor overall survival [9]. NEAT1 is another up-regulated lncRNA in cholangiocarcinoma whose expression has been increased parallel with expression of PTP4A1. On the other hand, expression of miR-186-5p has been found to be downregulated in these tissues. Expression levels of NEAT1 have been negatively correlated with survival of patients with cholangiocarcinoma, while being positively correlated with serum levels of CA-199 and lymph node metastasis. Mechanistically, NEAT1 serves as a sponge for miR-186-5p to up-regulate PTP4A1 levels. NEAT1 silencing or miR-186-5p over-expression has similarly suppressed proliferation ability, migration and invasiveness of cholangiocarcinoma cells, while suppression of miR-186-5p has reversed the impacts of NEAT1 silencing. Furthermore, NEAT1 has been shown to increase activity of PI3K/AKT signaling and influence epithelial-mesenchymal transition (EMT) of cholangiocarcinoma cells via the miR-186-5p/PTP4A1 route [10]. Expression of MALAT1 has also been upregulated in hilar cholangiocarcinoma tissues and cell lines in association with pathological T stage, tumor dimensions, and perineural invasion. Mechanistically, MALAT1 influences proliferation, migration, and invasion of hilar cholangiocarcinoma cells through sponging miR-204 and regulating

Table 2
Down-regulated lncRNAs in cholangiocarcinoma.

LncRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
CASC2	HuCCT1, RBE, CCLP, QBC939	–	miR-18a/ SOCS5	CASC2 represses cell growth metastasis and EMT.	[76]
FENDRR	QBC939, SSP-25, HuCCT1, RBE, HIBEC	–	Survivin	FENDERR reduces CCA cell growth, migration and invasion via restriction of surviving.	[77]
MEG3	CCLP1, QBC939	–	Bmi1/RNF2	MEG3 suppressed tumor growth in part by regulating polycomb repressive complex 1.	[78]
MT1JP	HCCC-9810, RBE, HuCCT1	Wnt/β-catenin	miR-18a-5p/ FBP1	MT1JP reduced proliferation migration invasion and tumorigenesis.	[79]
LINC01714	HuCCT1, CCLP1	–	FOXO3	LINC01714 is shown to be downregulated often in CCA and to predict the survival of patients. LINC01714 inhibited cancerous cell growth.	[80]
LncRNA-NEF	HuCCT1, TFK1	–	RUNX1	Increased levels of lncRNA-NEF reduced RUNX1 production in IHCC cell lines as well as migration and invasion.	[81]
MIR22HG	RBE, CCLP1, HuCCT1, QBC939, HIBEC	Wnt/β-catenin	–	By hindering the Wnt-catenin signaling pathway, MIR22HG diminished cell growth in CCA.	[82]
AC138430.1 AP001783.1	–	Nicotinate and nicotinamide metabolism Butanoate metabolism Regulation of autophagy Pantothenate and COA biosynthesis	–	This signature confidently predicted clinical outcome in patients with ICCA.	[21]

expression of CXCR4 [11].

3. Down-regulated lncRNAs

A number of lncRNAs have also been shown to act as tumor suppressors in cholangiocarcinoma. These lncRNAs have been shown to be down-regulated in cholangiocarcinoma cells and tissues as compared with controls (Table 2). Forced over-expression of these lncRNAs has reduced invasive properties of cholangiocarcinoma cells. CASC2 is an example of these lncRNAs. Up-regulation of CASC2 has suppressed proliferation, invasion and migration of QBC939 cells, while its silencing has augmented growth and metastatic ability of HUCCT1 cells. Moreover, miR-18a has been identified as a target of CASC2 through which CASC2 regulates expression of SOCS5 and affects EMT progression [76]. FENDRR is another downregulated lncRNA in cholangiocarcinoma tissues and cells. Expression of this lncRNA has been negatively correlated

Table 3
Up-regulated circRNAs in cholangiocarcinoma.

CircRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
CircRTN4IP1	–	–	miR-541-5p/ HIF1A	CircRTN4IP1 knockdown decreases ICC cell malignancy through the miR-541-5p/HIF1A axis.	[86]
Circ_0000591	–	TLR4/MyD88/IL6 pathway	miR-326	Circ_0000591 can increase CCA cell growth and carcinogenesis. Circ_0000591 works by sponging miR-326.	[87]
Circ_0020256	THP-1, HEK293, HCCC-9810, RBE	–	miR-432-5p/ E2F3	Circ_0020256 is transported to CCA cells by TAM-secreted (tumor-associated macrophages) exosomes.	[88]
Circ-ZNF609	HIBEC, CCLP-1, TFK-1, QBC939	–	miR-432-5p/ LRRC1	In CCA, circ-ZNF609 may aid tumor growth.	[89]
circHMGCS1–016	RBE, HCCC-9810, HUCCT1, QBC939	–	miR-1236-3p/ CD73 and GAL-8	Upregulation of circHMGCS1–016 facilitates ICC growth by increasing tumor cell invasiveness.	[90]
CircACTN4	HIBEpiC, RBE, QBC939, FRH0201	Hippo and Wnt signaling pathways	miR-424-5p/ YAP1	By engaging YBX1 to trigger FZD7 production, strong circACTN4 expression in ICC aids tumor initiation and progression.	[91]
Circ0021205	HIBEC, HCCC-9810, Huh-28, KMBC	–	miR-204-5p/ RAB22A	Circ0021205 increases CCA advancement via the miR-204-5p/ RAB22A axis.	[92]
Circ-LAMP1	HCCC-9810, RBE, Huh-28, QBC939, HuCCT1, CCLP1, HIBEC	–	miR-556-5p and miR-567/YY1	CCA cell growth is modulated by circ-LAMP1.	[93]
circDNM3OS	–	–	miR-145-5p/ MORC2	CircDNM3OS increased tumor formation, facilitating aggressiveness in CCA cells.	[94]
Circ_0005230	HCCC-9810, RBE, HIBEC, KMBC, HuCCT1, QBC939	–	miR-1238 and miR-1299	The amount of circ_0005230 in CCA tissues is linked to the disease severity.	[95]
Circ-0000284	TFK-1, SNU-869, SSP-25, RBE, HuCCT1, HuH28, H69	–	miR-637/LY6E	Exosome-transmitted circ-0000284 may promote malignant activity in nearby normal cells by increasing migration and proliferation while suppressing apoptosis.	[96]
Circ-CCAC1	CCLP1, QBC939	miR-514a-5p/ YY1/CAMLG signaling	miR-514a-5p/ YY1 and CAMLG	Circ-CCAC1 is a key player in CCA tumor growth.	[97]
CircRNA_000585	–	miR-615-5p/ AMOT/YAP pathway	miR-615-5p/ AMOT and YAP	CircRNA_000585 may be a useful biomarker or therapeutic option.	[98]
CDR1as	HIBEpiC, HCCC-9810, RBE	AKT3/mTOR signaling pathway	miR-641/AKT3	CDR1as may function as an oncogene in CCA.	[27,99]

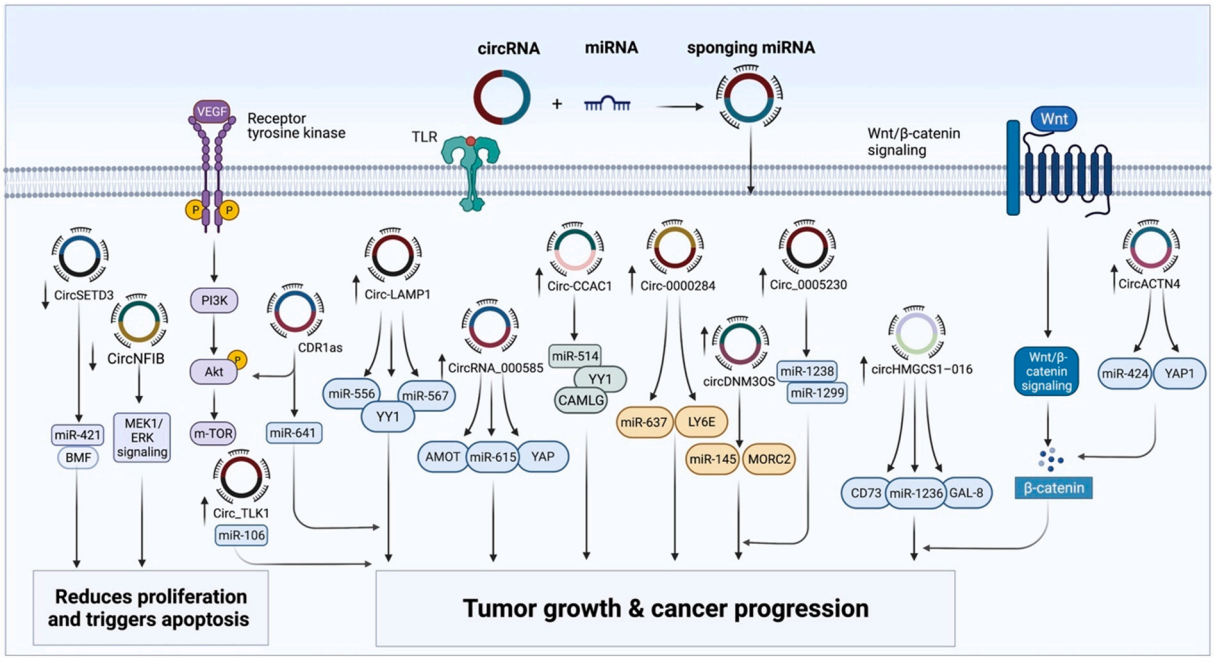

Fig. 2. Many different signaling pathways are activated by miRNA sponges, which influence the course of cholangiocarcinoma progression.

with expression levels of survivin (Fig. 1). From a mechanistical point of view, FENDRR suppresses proliferation, migration and invasive properties of cholangiocarcinoma cells through regulation of expression of survivin. This lncRNA has a functional association with SETDB1 and H3K9 which results in silencing of survivin expression [77]. MEG3 has also been shown to be significantly downregulated in cholangiocarcinoma samples in association with advanced TNM stage, lymph node involvement, and poor clinical outcomes. Up-regulation of MEG3 has resulted in suppression of cholangiocarcinoma growth in vitro and in xenograft models. Moreover, over-expression of MEG3 has suppressed migration and invasive properties of cholangiocarcinoma cells through reversing EMT. This lncRNA could affect expression of Bmi1 and RING finger protein 2. In fact, tumor suppressive effects of MEG3 are partly mediated through modulation of polycomb repressive complex 1 [78].

4. Up-regulated circRNAs

CircRNAs are another group of transcripts which are typically produced via back-splicing or exon skipping of pre-mRNAs, a distinctive process from canonical splicing. The continuous closed loop configuration of circRNA is principally made through joining of a downstream 3′ splice site with an upstream 5′ splice site [83]. These transcripts have fundamental roles in the regulation of gene expression and their expressions have been found to be altered during carcinogenesis [84,85]. Several circRNAs have been demonstrated to act as oncogenic factors in cholangiocarcinoma (Table 3) (Fig. 2). For instance, circRTN4IP1 has been shown to regulate the malignant properties of these cells through sponging miR-541-5p and sunsequent induction of HIF1A production [86]. Circ_0000591 is another oncogenic circRNA that serves as a molecular sponge for miR-326 to enhance cholangiocarcinoma progression through the TLR4/MyD88/IL-6 axis [87]. Circ_0020256 is another circRNA being present in exosomes of tumor-associated M2 macrophages (TAMs). The induced TAMs have been shown to promote proliferation, migration, and invasive aptitude of cholangiocarcinoma cells through secretion of exosomes. Circ_0020256 has significantly enhanced cellular activity through interaction with miR-432-5p. siRNA-mediated silencing of circ_0020256 has suppressed proliferation, migratory aptitude, and invasiveness of cholangiocarcinoma cells both in vitro and in vivo. Cumulatively, circ_0020256 produced by TAM-originated exosomes can enhance tumorigenic properties of cholangiocarcinoma cells through miR-432-5p/E2F3 axis [88].

5. Down-regulated circRNAs

A number of other circRNAs have been shown to exert anti-cancer effects (Fig. 2). These circRNAs have been typically down-regulated in cholangiocarcinoma cells and tissues (Table 4). CircSETD3 is an example of these circRNAs. It can inhibit cell proliferation and induce apoptosis through sponging the oncogenic miRNA miR-421 [100]. Similarly, circNFIB has been found to exeert its tumor suppressor role via inhibiting MEK1/ERK signals in intrahepatic cholangiocarcinoma [101]. Few

Table 4
Down-regulated circRNAs in cholangiocarcinoma.

CircRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
CircSETD3 (hsa_circ_0000567)	HiBECs, HUCCT1, TFK1, QBC939	–	miR-421/ BMF	miR-421/BMF axis is controlled by circSETD3.	[100]
CircNFIB	HuCCT1, HCCC9810, RBE	MEK1/ERK signaling	–	Through modulation of ERK signaling, CNFIB acts as a tumor suppressor, inhibiting ICC growth and metastasis.	[101]
Hsa_circ_0001649	HCCC-9810, RBE, CCLP1, HuCCT1, Huh-28, KMBC, QBC939, HIBEC	–	–	Has_circ_0001649 has been shown to be downregulated in CCA tissue specimens and cell lines, which might be linked to aggressive CCA phenotypes.	[103]
SMARCA5	TFK-1, HuH-28	–	–	In ICC, circSMARCA5 is downregulated in tumor tissues.	[102]

Table 5
Up-regulated miRNAs in cholangiocarcinoma.

miRNA	Assessed cell line	Pathways	Targets/regulators	Function	Reference
miR-196-5p	HIBEC, HuCCT1, QBC939, Huh-28	Wnt/β-catenin	HAND1	By restoring HAND1 expression, reducing miR-96 production might limit abnormal cell growth and metastasis.	[106]
miR-23a-3p	QBC939, HUCCT1, RBE, HCCC9810, HiBEC	–	DNM3	Inhibiting miR-23a-3p can stop CCA from progressing. Exosomal miR-23a-3p promotes CCA cell proliferation.	[107]
miR-155-5p	TFK-1, HUCCT-1,	RAF/MEK/ERK pathway	SOX1	miR-155-5p which has been elevated in CCA, inhibits SOX1 production, facilitating CCA growth by activating the RAF/MEK/ERK signaling pathway.	[108]
miR-181b-5p	–	PI3K/AKT signaling pathway	PARK2	miR-181b-5p behaved as an oncogene in CCA by boosting tumor growth.	[109]
miR-192-5p	HIBECs, TFK-1, CCLP-1, HCCC 9810, RBE, HuCCT-1	MEK/ERK signaling pathway	–	Through stimulation of the MEK/ERK signal transduction pathway, miR-192-5p boosted CCA cell growth.	[110]
miR-27a	HuCCT1, RBE, HuH28, QBC939, HIBEpic	–	–	Elevated levels of miR-27a boost the growth of CCA cells.	[111]
miR-19b-3p	HUCCT1, RBE, CCLP-1, TFK-1, HIBEpiC	–	CCDC6	The blood level of miR-19b-3p is an important molecule for ICC detection.	[112]
miR-30a-5p	HCCC9810, QBC939, RBE, HUCCT1, HiBEC	JAK/STAT pathway	SOCS3	Cell growth is slowed and cell death is triggered when miR-30a-5p is hindered.	[113]
miR-96	HuCCT1, HuH28, RBE, HIBEC	PI3K/AKT signaling pathway	MTSS1	miR-96 is linked to metastases and TNM stage in CCA.	[114]
miR-30d-5p miR-92a-3p	–	–	–	In CCA, the production of miR-30d-5p and miR-92a-3p is much increased.	[115]
miR-25	CCLP1, HuCCT1, HIBEC	–	–	Increased expression of miR-25 has been related to a bad prognosis in CCA patients.	[116]
miR-142-5p	–	–	PTEN	In ICC, plasma miR-142-5p is highly elevated.	[117]
miR-10a-5p	CCLP1, SG-231, HIBEC	PTEN-Akt pathway	PTEN	miR-10a-5p suppression inhibits CCA cell growth via inhibiting the Akt pathway.	[118]
miR-191	QBC939, HUH28, HuCCT1, RBE, CCLP1, TFK1, HiBECs	Wnt/β-catenin signaling	sFRP1	miR-191 knockdown prevents tumor cells from surviving and causes them to die.	[119]
miR-383	RBE, HuCCT1, QBC939, CCLP, HIBEpic	–	IRF1	Through direct suppression of IRF1, miR383 lowers CCA cell growth. Furthermore, miR-383 has been linked to a bad prognosis.	[120]
miR-122 miR-192 miR-29b miR-155	–	–	–	Patients with CCA have increased serum amounts of these 4 miRNAs.	[121]
miR-92b	–	–	DAB2IP, SPHK2, NFIA, USF2, SLC12A5, BCL2L11, TRAF3, ZDHHC3, RNF44, TCF21, MYO18A, PER2, TSC1, KLF2, E2F3, ARRDC4, PAPOLB	miR-92b is linked to worse outcomes in CCA patients.	[122]
miR-193-3p	ICC-9810, HIBEC	–	TGFBR3	CCA cell growth is inhibited by miR-193-3p reduction.	[123]
miR-21	–	–	–	For the screening of end-stage CCA, plasma miR-21 looks to be a viable biomarker.	[124]
miR130a-3p	CCLP-1, MzChA-1	–	PPARG	Via PPARG, miR-130a-3p is linked to gemcitabine response in CCA.	[125]
miR-29a	–	–	–	The transcription of miR-29a is augmented with CCA growth, and may serve as a predictive factor in CCA patients.	[126]
miR-24	Mz-ChA-1, TFK-1, SG231, CCLP-1, HuCC-T1, HuH-28	–	Menin	Alteration of miR-24 increases CCA spread, mobility and vasculature via altering the transcription of genes involved in the cell cycle and cell death.	[127]

studies have evaluetd the consequences of down-regulation of tumor suppressor circRNAs in cholangiocarcinoma. Among these studies is the study conducted by Lu et al. which highlights the impact of circRNA SMARCA5 expression in confering favorable clinical outcome and enhancing sensitivity to chemotherapeutic agents in intrahepatic cholangiocarcinoma [102].

6. Up-regulated miRNAs

Recent studies revealed that miRNAs control oncogenes and tumor suppressor genes and are altered in human malignancies [104,105]. Several miRNAs have been shown to be dysregulated in cholangiocarcinoma (Table 5). Many of these miRNAs are targets of lncRNAs and circRNAs and their expression is dysregulated as a consequence of dysregulation of these transcripts. miR-196-5p is an example of oncogenic miRNAs in cholangiocarcinoma which enhances proliferation and migration of these cells through regulation of HAND1/Wnt/β-Catenin pathway [106] (Fig. 3). miR-23a-3p is another oncogenic miRNA being secreted by exosomes. This miRNA acts in favour of cancer progression through interacting with Dynamin3 [107]. Moreover, miR-155-5p has been found to suppress expression of SOX1 to increase cell proliferation through RAF/MEK/ERK pathway [108]. Other examples of these miRNAs are shown in Table 5.

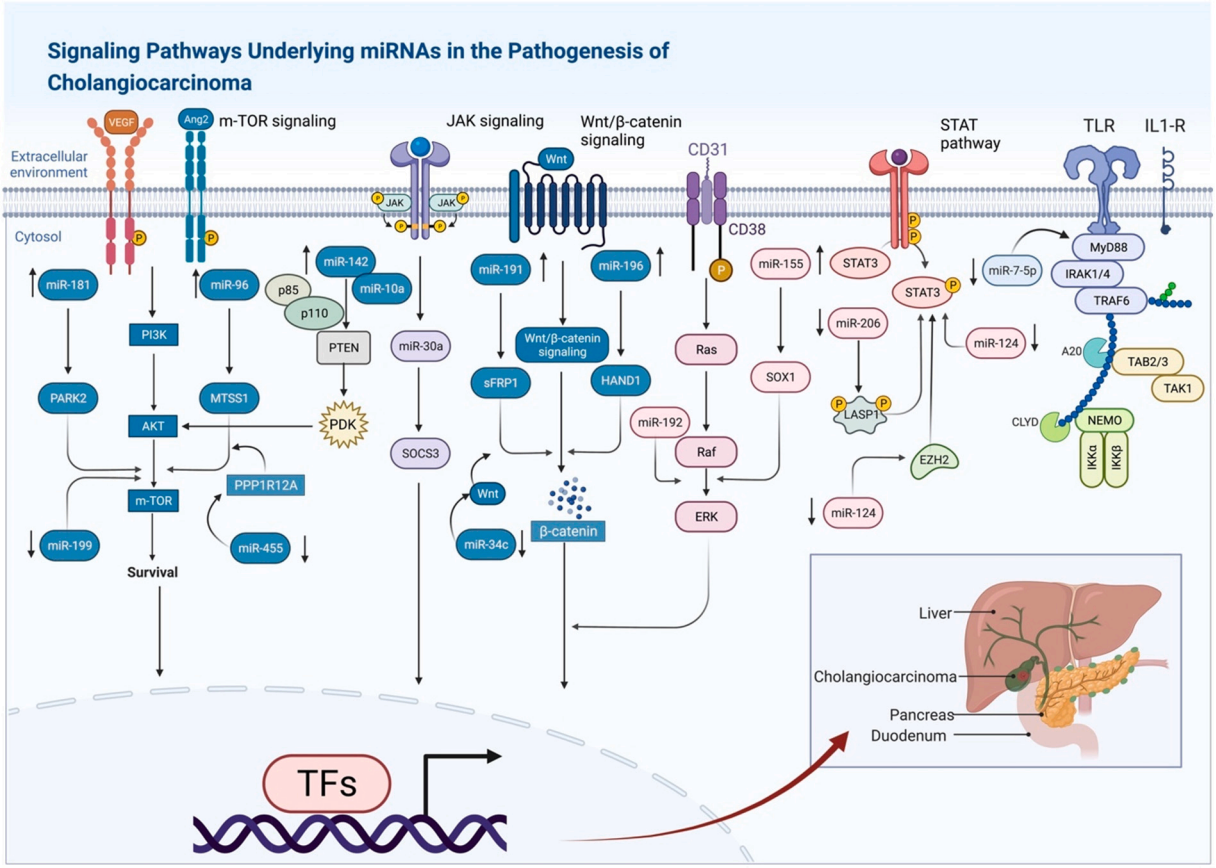

Fig. 3. The progression of cholangiocarcinoma is associated with the involvement of a number of separate signaling pathways that are controlled by miRNAs.

7. Down-regulated miRNAs

Similar to other groups of non-coding RNAs, tens of miRNAs have been found to exert anti-cancer effects in cholangiocarcinoma (Table 6). For instance, miR-28-5p has been identified as an inhibitor of cholangiocarcinoma progression whose expression can predict favorable clinical outcome in this type of cancer [128]. Similarly, miR-15a-5p is a tumor suppressor miRNA being produced by umbilical cord mesenchymal stem cells and transfers to other cells through their exosomes. This miRNA can inhibit progression of cholangiocarcinoma through suppression of CHEK1 expression [129]. In addition to these miRNAs, miR-206 has been shown to suppress progression of intrahepatic cholangiocarcinoma and promote chemo-sensitivity through suppression of cancer cell interaction with stromal cancer-associated fibroblasts [130]. Other examples of this kind o miRNAs are presentaed in Table 6.

8. Discussion

Although being rare tumors, cholangiocarcinomas are challenging due to complex pathological changes, clinical manifestations and lack of efficient therapeutic options. Thus, identification of appropriate biomarkers and therapeutic targets for cholangiocarcinoma has a practical significance. Numerous non-coding RNAs from different classes of these transcripts have been shown to be dysregulated in cholangiocarcinoma, therefore being suggested as potential targets for early detection of this cancer.

Mechanistically, lncRNAs and circRNAs can act as molecular sponges for small-sized non-coding RNAs, i.e. miRNAs to affect expression of miRNAs targets. NEAT1/miR-186-5p, MALAT1/miR-204, TM4SF1-AS1/miR-744-3p, LINC00630/miR-199a, TMPO-AS1/let-7 g-5p, PSMA3-AS1/miR-3761-3p, TUG1/miR-29a, PCAT6/miR-330-5p, SNHG16/miR-146a-5p, lnc-ATB/miR-200c, HOTAIR/miR-204-5p, RHPN1-AS1/miR-345-5p, DANCR/miR-345-5p, SNHG1/miR-140, ST8SIA6-AS1/miR-145-5p, FLVCR1-AS1/miR-485-5p, FAM66C/miR-23b-3p, SNHG12/miR-199a-50 and LINC00184/miR-23b-3p are examples of lncRNA/miRNA pairs that are involved in the pathogenesis of cholangiocarcinoma. Similarly, several circRNA/miRNA pairs such as circRTN4IP1/miR-541-5p, circ_0000591/miR-326, circ_0020256/miR-432-5p, circ-ZNF609/miR-432-5p, circHMGCS1–016/miR-1236-3p, circACTN4/miR-424-5p, circ0021205/miR-204-5p, circLAMP1/miR-556-5p, circDNM3OS/miR-145-5p, circ_0005230/miR-1238 and circ0000284/miR-637 have been found to affect carcinogenesis process in this type of cancer. All of these molecular axes in addition to other identified and unidentified lncRNA/miRNA and circRNA/miRNA pairs represent potential targets for therapeutic options, since they can affect fundamental aspect of carcinogenesis, such as cell proliferation, differentiation and apoptosis.

Although several studies have indicated dysregulation of non-coding RNAs in cholangiocarcinoma, their application as diagnostic markers in this type of cancer has not been completely investigated. Since these transcripts can be detected in biofluids, they might be used as targets for non-invasive methods of cancer detection. Moreover, the stability of both miRNAs and circRNAs in the circulation of patients provides an additional advantage for these transcripts in diagnostic and prognostic approaches.

It is worth mentioning that the cross-talks of lncRNAs, circRNAs, and miRNAs are very complex and additional transcription factors are involved in this type of cross-talk. To unravel the role of these non-coding RNAs in the pathogenesis of cholangiocarcinoma, it is necessary to conduct high throughput sequencing experiments in different stages of this cancer to identify stage-specific changes that can promote progression of cholangiocarcinoma. Moreover, studies should focus on a

Table 6
Down-regulated miRNAs in cholangiocarcinoma.

miRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
miR-28-5p	–	–	CD44	The production of miR-28-5p is lowered in CCA and is linked to a bad prognosis.	[128]
miR-15a-5p	HuCCT1, HuH28	–	CHEK1	The miR-15a-5p/CHEK1 axis plays a critical role in the evolution of CCA.	[129]
miR-206	HiBEC, HUCCT1, RBE, HUVECs, 293 T	STAT3 pathway	LASP1	The anticancer action of miR-206 is achieved by reducing the aggressiveness of tumor cells and stromal fibroblasts.	[130]
miR-7-5p	HCCC-9810, HuCCT1, QBC-939, RBE, HIBEC	IRAK4/TRAF6/NF-κB signaling pathways	MyD88	miR-7-5p decreased tumor growth by attacking MyD88, suggesting that miR-7-5p and MyD88 could be possible targets for reducing ICC metastasis.	[131]
miR-92a-3p	HIBEC, HCCC-9810, RBE	Notch signaling pathway	NOV	miR-92a-3p-mediated NOV overexpression may increase cholangiocarcinoma cell motility and invasion.	[132]
miR-146b-5p	HUCCT-1	–	TRAF6	miR-146b-5p is a CCA silencer which interacts TRAF6 and impedes cancer growth.	[133]
miR-34c	HuCCT-1, CCA; QBC939, CCC-HSF-1, HIBEC	Wnt signaling pathway	WNT1	miR-34c inhibits tumor growth.	[134]
miR-455-5p	FK-1, HCCC9810, HEK 293 T cells (CRL-3216)	MAPK and PI3K/AKT pathway	PPP1R12A	By targeting PPP1R12A, miR-455-5p stops CCA cells from proliferating, migrating or invading.	[135]
miR-1182 let-7a	HIBEPIC, CCC-5, HCC-9810, Huh28	–	NUAK1	miR-1182 and let-7a have inhibitory impacts on tumor growth, and a boosting impact on cell autophagy through the down-regulation of NUAK1 production.	[136]
miR-126-3p	–	–	–	CCA is linked to a lack of miR-126-3p production.	[137]
miR-29b	QBC939, HIBEC	–	DNMT3B	By inhibiting DNMT3B production, miR-29b works as a tumor suppressor in CCA.	[138]
miR-144-5p miR-451a	HuCCT-1, HCCC-9810, RBE	–	ST8SIA4	Boosted expression level of miR-144-5p and miR-451a hindered tumor growth via reducing the production of ST8SIA4.	[139]
miR-874	QBC939, RBE	NF-κB pathway	CCNE1	miR-874 hindered EMT in CCA through adversely influencing CCNE1 and blocking the NF-κB pathway.	[140]
miR-885-5p	HuCCT1, RBE, Huh28	AKT signaling pathway	IGF2BP1 and GALNT3	By modulating GALNT3 and IGF2BP1, miR-885-5p affects iCCA growth.	[141]
miR-129-2-3p	QBC-939, RBE, BEC	MMP-2 signaling pathway	Wip1	Reduced miR-129-2-3p production is linked to malignant clinical manifestations in ICC patients. Moreover, miR-129-2-3p plays an antitumor function in ICC growth.	[142]
miR-373	RBE, QBC939, HCCC9810, HUCCT-1, HIBEpiC	–	ULK1	In CCA, miR-373 diminishes ULK1 production, hinders autophagy and boosts cell death.	[143]
miR-148a	HuCCT1, RBE	–	GLUT1	In the growth of iCCA, irregular transcription of the miR-148a is critical.	[144]
miR-137	TFK-1, HuCCT1, RBE, QBC939, HIBEpiC	Wnt signaling pathway	WNT2B	Through lowering the transcription of WNT2B, miR-137 functions as a suppressor in CCA, hindering cell growth.	[145]
miR-194	QBC-939	Rho pathway	ECT2	Upregulation of miR-194 impeded CCA stem cell activities by inactivating the Rho pathway, indicating that the miR194/ECT2/Rho axis might be a new treatment option.	[146]
miR-876	H69, HuCCT1, KMCH, KMBC, HuH28	–	BCL-XL	Elevated expression of miR-876 hindered BCL-XL transcription, CCA cell growth and caused cell death.	[147]
miR-424-5p	CCLP-1, RBE, HuCCT-1, HIBEC	mTOR pathway.	ARK5	miR-424-5p production can drastically lower ICC cell growth. miR-424-5p may have a part in the evolution of ICC. For ICC therapy, miR-424-5p might be a decent choice.	[148]
miR-551b-3p	HuCCT-1, RBE, HCCC-9810, QBC939, HiBEC	–	CCND1	miR-551b-3p reduces CCA cell growth, slows cell cycle progression and triggers apoptosis.	[149]
miR-186	CCLP1, SG-231, HIBEC	–	Twist1	Elevated transcription of miR-186 hindered cell growth in CCA.	[150]
mir-637	QBC939	–	CTSB	The growth of CCA cells is greatly altered by miR-637. miR-637 has a potent inhibitory effect on CTSB expression.	[151]
miR-195	–	–	–	The plasma of CCA sufferers has lower transcript levels of miR-195. Plasma miR-195 can be utilized as a precise screening indicator.	[152]
miR-30e	MMNK-1, HuCCT1, HuH28, OZ, TFK-1, RBE	–	Snail	Snail is a direct target of miR-30e that can block EMT by preventing CCA cell growth.	[153]
miR-124	BEC, 293 T, HuCCT1, KMBC, MZChA1	STAT3 signaling pathway	EZH2 and STAT3	miR-124 performs a tumor inhibitory effect in CCA. Reduced transcription of miR-124 is linked to tumor growth.	[154]
miR-433 miR-22	H69, NHC, HuCCT-1, KMCH	MAPK and Hh pathways	HDAC6	In CCA cell line, induction of mir-433 or mir-22 reduces growth.	[155]
miR-26b-5p	RBE, HCCC-9810	–	S100A7	By targeting S100A7, miR-26b-5p prevents ICC cells from proliferating migrating and invading.	[156]
miR-622	QBC-939, H69	–	c-Myc	Via specifically targeting c-Myc, miR-622 affects CCA cell growth, motility and penetration.	[157]
miR-16	HUCCT1, RBE, 9810, QBC-939, HiBEC	–	YAP1	A feasible treatment option for CCA may be miR-16 that operates as a tumor suppressor in CCA by inhibiting YAP1.	[158]
miR-106b	KKU-M214P/R, KKU-M139P/R	–	zbtb7a	A new approach for CCA treatment is presented by miR-106b that can overcome 5-fu tolerance via zbtb7a suppression.	[159]
	ICC-9810, HUCCT1, RBE	–	SIP1	miR-590-3p blocks ICC EMT process and reduces ICC cell growth.	[160]

(*continued on next page*)

Table 6 (*continued*)

miRNA	Assessed cell line	Pathways	Targets/ regulators	Function	Reference
miR-590-3p					
miR-124	QBC939, RBE	–	GATA6	miR-124 reduces the transcription of GATA6, which in turn prevents the growth of CCA cells.	[161]
miR-199a-3p	RBE, GBC-SD	mTOR signaling pathway	mTOR	By blocking the mTOR pathway, miR-199a-3p can boost the cisplatin sensitivity of CCA cells.	[9]
miR-26a	RBE, HCCC-9810	–	KRT19	KRT19 may be down-regulated by miR-26a.	[162]
miR-122	QBC939	–	P53	Cell death is triggered and tumor growth is prevented by upregulating miR-122.	[163]

group of non-coding RNAs instead of individual ones to assess function of these transcripts in a more comprehensive way.

The studies summarized above lack the system biology approach to identify the most important modules in the pathogenesis of cholangiocarcinoma. Moreover, those aimed at identification of biomarkers for this type of cancer did not design a panel of non-coding RNAs that could detect cholangiocarcinoma in early stages. Moreover, there is no clinical study on efficiency and safety of proposed non-coding RNAs-targeting strategies.

Future studies are needed to elaborate the functional consequences of modulation of expression of these non-coding RNAs in animal models of cholangiocarcinoma in order to pave the way for introduction of these modalities in clinical settings.

CRediT authorship contribution statement

SGF wrote the manuscript and revised it. MT designed and supervised the study. AS, MS and BMH collected the data and designed the tables and figures. All authors read and approved the submitted manuscript.

Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication

Not applicable.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Declaration of competing interest

The authors declare they have no conflict of interest.

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