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Review Article

Non-coding RNA and Drug resistance in cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma is a highly aggressive cancer with a dismal prognosis and limited resectability. Chemotherapy has demonstrated tremendous benefits for patients with advanced and inoperable cancer, but drug resistance poses a significant obstacle. Despite recent progress in cancer therapy, the mechanisms driving drug resistance are multifaceted and not completely comprehended. Non-coding RNA refers to RNA molecules that are endogenous and do not code for proteins. Particularly microRNAs, long non-coding RNAs, circular RNAs, are widely acknowledged to be involved in cancer initiation, proliferation, and metastasis. Recently, evidences suggests that abnormal expression of non-coding RNAs contributes to resistance to different type of cancer therapies in cholangiocarcinoma. This occurs via the rewiring of signaling pathways including the reduction of anticancer drugs, apoptosis, interaction between cholangiocarcinoma and tumor-infiltrating immune cells, and cancer stemness. Thus, our review aims to demonstrate the potential of targeting non-coding RNA to override drug resistance and summarize the molecular mechanisms of how non-coding RNA contributes to drug resistance in cholangiocarcinoma.

1. Background

Cholangiocarcinoma, or CCA, is an aggressive cancer that originates from the cells lining the bile ducts. These bile ducts are part of the biliary tree, which includes both intrahepatic and extrahepatic ducts, as well as the common bile duct, hepatic ducts, and smaller bile ducts within the liver. CCA may arise in any part of the biliary tree, which encompasses the intrahepatic, perihilar, or distal bile ducts [1]. Accumulated evidence suggests a worldwide increase in CCA incidence. This trend has been observed in various regions across the globe [2]. The prognosis for patients with CCA is exceedingly grim. One of the chief obstacles in enhancing CCA outcomes is the paucity of early warning signs, which frequently results in late-stage detection. Consequently, a sizable percentage, approximately 70–80 %, of patients are diagnosed after the cancer has progressed to an advanced stage [3]. The prognosis for CCA is extremely poor, with less than 5 % of diagnosed patients surviving for at least five years. The low survival rate underscores the disease's aggressive nature and treatment-related challenges. Anticancer drugs have made noteworthy strides in increasing overall survival rates for CCA patients. These medications, such as chemotherapy, targeted therapy drugs, and immune checkpoint inhibitors, indicate significant outcomes in expanding life expectancy and ameliorating the quality of life for some patients. However, drug resistance remains a significant challenge in the treatment of CCA. Despite the initial response to therapy, many patients eventually develop resistance to the medications, leading to disease progression and limited treatment options. Therefore, it is crucial to understand the mechanisms underlying drug resistance for developing strategies to overcome this obstacle (see Tables 1–7, Fig. 1).

Gemcitabine, cisplatin, 5-fluorouracil (5-FU), and capecitabine are commonly used chemotherapy medications for treating CCA in both advanced and post-operative settings. These medications should be considered as standard treatment options for patients with CCA. Capecitabine serves as an adjuvant therapy for postoperative patients suffering from CCA to reduce the chances of cancer recurrence [4]. In the context of advanced and unresectable CCA, the preferred initial systemic chemotherapy typically utilizes a gemcitabine and cisplatin combination [5]. Meanwhile, patients who exhibit poor mismatch repair (MMR), high microsatellite instability (MSI), and high levels of PD-L1 expression have been identified as potential candidates for benefiting from immunotherapy [6]. Targeted drugs have demonstrated promise in the treatment of CCA. Notably, Pemigatinib, Ivosidenib, and Trametinib target specific genetic alterations present in CCA tumors [6]. However, drug resistance poses a considerable obstacle in cancer treatment and can lead to cancer recurrence and refractory disease. Numerous genes linked to chemoresistance have been identified by researchers. These genes are classified into various mechanisms of chemoresistance (MOC),

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Table 1
Oncogenic miRNAs and gemcitabine resistance in CCA.

miRNA	Expression	Gene and Pathway	Mechanism	Reference
miR-21	up	PTEN, PI3K/AKT	MOC-1b and MOC-5b	[22,25]
miR-130a-3p	up	PPARα, PPARγ	MOC-4	[26,27]
miR-200b	up	PTPN12, Src	MOC-5b	[22]
miR-210	up	HIF-3α	MOC-5b	[28,29]
miR-210	up	RECK	MOC-5b	[30]
miR-181c	up	NDRG2	MOC-5b	[31,32]
let-7a	up	NF2/Stat3	MOC-5b	[33]
miR-1249	up	FZD8	MOC-7	[34]
miR-125a-5p	up	–	unknown	[35]

Table 2
Tumor suppressive miRNAs and gemcitabine resistance.

miRNA	Expression	Gene and Pathway	Mechanism	Reference
miR-29b	down	PIK3R1, MMP-2	MOC-5a and MOC-6	[35]
miR-221	down	PIK3R1	MOC-5a	[35]
miR-637	down	LASP1	MOC-5a	[40,41]
miR-205	down	MMP2	MOC-6	[35,42]
miR-206	down	CAF	MOC-6	[43]
miR-424-5p	down	BCL9L	MOC-7	[44]
miR-520c-3p	down	MYCN/YAP1/TEAD2/SOX2	MOC-7	[45]
miR-149-5p	down	–	MOC-7	[46]

Table 3
MiRNAs and 5-FU resistance in CCA.

miRNA	Expression	Gene and Pathway	Mechanism	reference
miR-20a-5p	up	SHOC, ERK1/2	MOC-1b	[49]
miR-320	down	Mcl-1	MOC-5a	[50]
miR-204	down	Bcl-2	MOC-5a	[50]
miR-106b	down	Zbtb7a	MOC-5a	[51–53]
miR-328	down	GPAM	MOC-5a	[54]
miR-200 b/c	down	CSCs	MOC-7	[55]
miR-885-5p	down	MTPN	unknown	[56]

Table 4
MiRNAs and cisplatin resistance in CCA.

miRNA	Expression	Gene and Pathway	Mechanism	Reference
miR-199a-3p	up	mTOR/MDR1	MOC-1b	[60]
miR-637	down	LASP1	MOC-5a	[40,41]
miR-520c-3p	down	MYCN	MOC-7	[45]
miR-885-5p	down	MTPN	unknown	[56]

Table 5
MiRNAs and sorafenib resistance in CCA.

miRNA	Expression	Gene and Pathway	Mechanism	Reference
miR-141	up	hOCT1	MOC-1a	[68]
miR-330	up	hOCT1	MOC-1a	[68]
miR-138	down	SOX4	MOC-7	[69]

including MOC1-1a: reduced drug uptake, MOC-1b: enhanced drug export, MOC-2a: reduced prodrug activation, MOC-2b: enhanced drug inactivation, MOC-3: altered drug targets, MOC-4: enhanced DNA repair, MOC-5a: pro-apoptotic, MOC-5b: pro-survival, MOC-6: changes in tumor microenvironment, MOC-7: Phenotypic transition [7].

Table 6
LncRNAs and drug resistance in CCA.

lncRNA	Expression	Gene and Pathway	Mechanism	Reference
FALEC	up	miR-20a-5p/SHOC2	MOC-1b	[49,76]
LINC01714	down	FOXO3	MOC-4	[77,78]
lnc-PKD2-2-3	up	miR-328/GPAM	MOC-5b	[54]
HOTTIP	up	miR-637/LASP1	MOC-5b	[40,41]
HOXD-AS1	up	miR-520c/MYCN	MOC-7	[45]
LINC00665	up	miR-424/BCL9L	MOC-7	[44]
DLEU1	up	miR-149-5p/YAP1/TEAD2/SOX2	MOC-7	[46]
NEAT-1	up	–	unknown	[79]

Table 7
Circ-RNAs and drug resistance in CCA.

circ-RNA	Expression	Gene and Pathway	Mechanism	Reference
cNFIB	down	MEK1/ERK	MOC-3	[81]
SMARCA5	down	–	MOC-5a	[82,83]
HMGCS1-016	up	miR1236-3p/CD73, GAL8	MOC-6	[84]

Non-coding RNAs (ncRNAs) are a diverse collection of RNA molecules that lack the ability to encode proteins but perform crucial functions in a variety of biological processes. They can be grouped into numerous subtypes based on their length and structural characteristics, such as microRNA, small nuclear RNA, Piwi-interaction RNA, small nucleolar RNA, and long non-coding RNA [8–10]. Dysregulation of microRNAs (miRNAs) is commonly observed in cancer, and several miRNAs are upregulated in cancer cells, contributing to tumor progression [11]. In addition to up-regulated miRNAs acting as oncogenes, some miRNAs also function as tumor suppressors but are down-regulated in various tumor types. Failure to regulate key genes that control cell growth, invasion, and metastasis due to decreased expression of these tumor suppressor miRNAs could contribute to tumor progression [12,13]. Certainly, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) are capable of functioning as oncogenes or tumor suppressors in a variety of tumor types. These non-coding RNAs possess vital regulatory roles in the development and progression of cancer [14–17]. Recently, studies have shown that miRNAs, lncRNAs, and circRNAs play critical roles in regulating proliferation, invasion, and metastasis in CCA, as well as in the development of drug resistance. These non-coding RNAs are significant players in the molecular mechanisms driving drug resistance in CCA [18–20].

In this thorough examination, we seek to investigate the processes of biogenesis and regulation for ncRNAs and their connections with drug resistance in CCA.

2. miRNA and drug resistance

Currently, gemcitabine, cisplatin, 5-fluorouracil, and sorafenib are frequently administered in clinical settings. MiRNAs, ranging in size from 17 to 25 nucleotides, are a type of small non-coding RNA molecules that crucially contribute to gene regulation at the post-transcriptional level [21]. Extensive research has shown that dysregulation of miRNAs significantly contributes to CCA's development, proliferation, and metastasis [22,23]. Recent studies have provided compelling evidence that the dysregulation of multiple miRNAs is associated with drug resistance in CCA. These dysregulated miRNAs have been identified as key players in the acquisition and maintenance of drug resistance, contributing to treatment failure and disease progression [24].

2.1. *miRNAs related gemcitabine-resistance*

Gemcitabine has been widely utilized as a neoadjuvant, adjuvant,

and palliative treatment for CCA, whether as a single agent or in combination therapy [36]. However, the development of resistance to gemcitabine is a significant challenge for many patients in their treatment of CCA. Various studies have implicated several miRNAs in the development of gemcitabine resistance in CCA. These oncogenic miRNAs modulate cellular response to gemcitabine treatment, leading to reduced drug sensitivity and resistance. The miRNAs involved in this effect include miR-21, miR-130a-3p, miR-200b, miR-210, miR-181c, miR-1249, and miR-125a-5p.

Studies have revealed significant insights into the molecular mechanisms by which particular oncogenic miRNAs contribute to gemcitabine resistance in CCA. It have been reported that miR-21 is an oncogenic microRNA. Overexpression of miR-21 in CCA leads to the downregulation of the tumor-suppressor gene, phosphatase and tensin Homolog (PTEN). Subsequently, this dysregulation leads to activation of the PI3K/AKT signaling pathway, which in turn promotes cell survival and resistance to gemcitabine-induced apoptosis [22]. Besides, PI3K/AKT pathway could induce expression of membrane transporters and decreased susceptibility to chemotherapy [25]. The study revealed that dihydromyricetin and galangin could inhibit miR-21, resulting in decreased CCA development by promoting apoptosis in CCA cells [37, 38]. MiR-130a-3p could promotes resistance to gemcitabine by suppressing the expression of PPARG, which are involved in nucleotide metabolism [26]. It was reported that PPARG have anti-tumor effects via

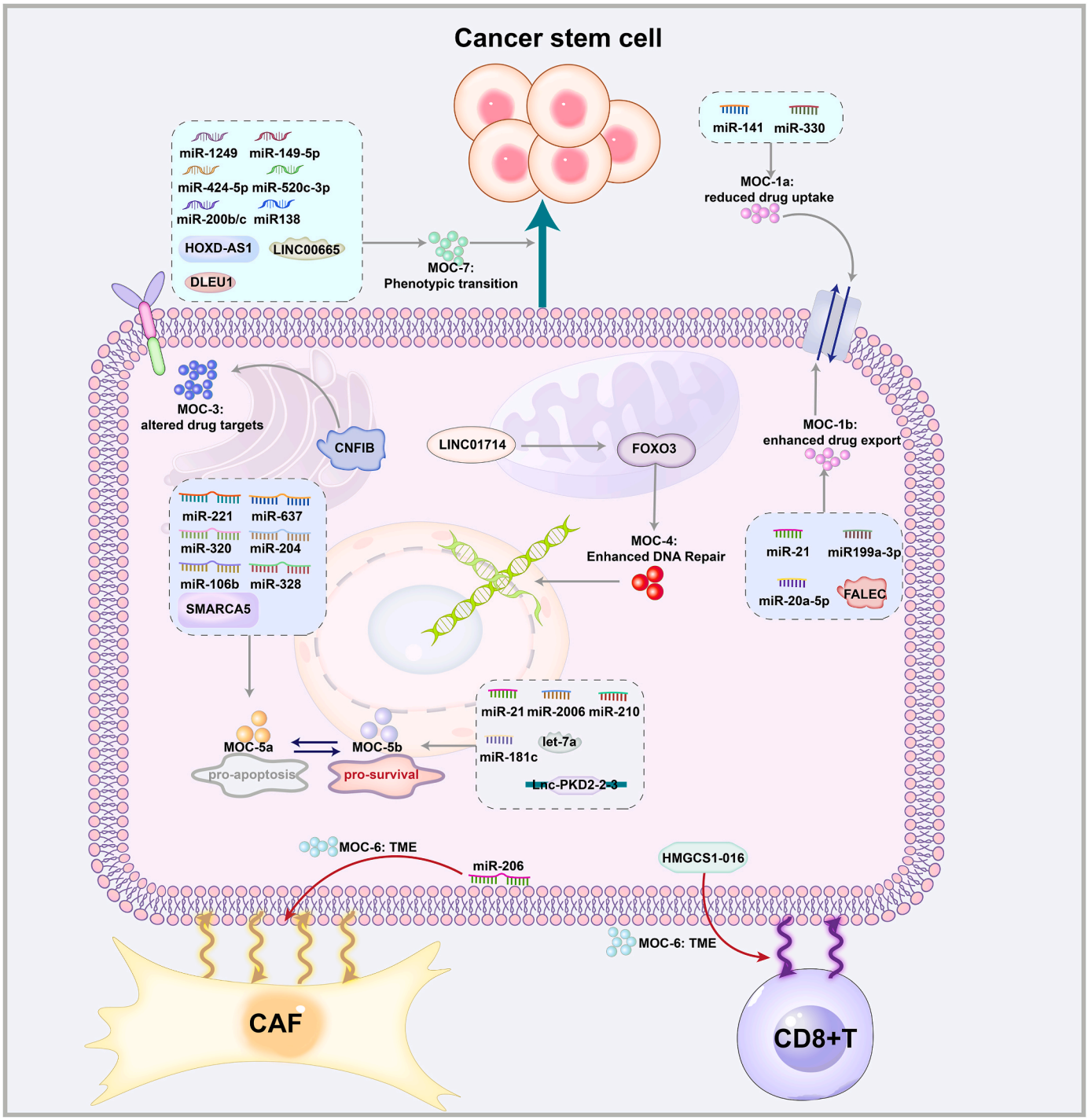

Fig. 1. Several miRNAs, LncRNAs, circRNAs were identified to be involved in drug resistance in CCA.

cell-cycle arrest and DNA-damage repair [27]. Interestingly, pioglitazone, which is a PPARγ agonist, is capable of reducing the expression of miR-130a-3p and thereby alleviating gemcitabine resistance. Several miRNAs play a part in resistance to gemcitabine by inhibiting apoptosis, including miR-200b, miR-210, let-7a, and miR-181c. Excessive expression of miR-200b in CCA could suppress PTP non-receptor type 12 (PTPN12), a phosphatase that negatively regulates the oncogene Src. By inhibiting PTPN12 expression, miR-200b contributes to resistance to gemcitabine via reduced apoptosis in CCA [22]. MiR-210 has been associated with a poor prognosis in CCA, and inhibiting endogenous miR-210 would improve gemcitabine sensitivity via HIF-1α [28]. In CCA, it was reported that HIF-1α promotes proliferation, invasion, and migration, while down-regulated HIF-1α enhances apoptosis [39]. Therefore, suppressed expression of HIF-3α, a negative regulator of HIF-1α, induced by miR-210, resulted in gemcitabine resistance. Additionally, it has been reported that miR-210 promotes CCA migration, metastasis, and resistance to gemcitabine by inhibiting the expression of RECK. MiR-181c was up-regulated in CCA and contributed to down-regulated N-myc downstream-regulated gene 2 (NDRG2), which could inhibit CCA proliferation, metastasis and gemcitabine resistance [31]. NDRG2 has been shown to enhance cisplatin-induced apoptosis via modulation of the Bak-Mcl-1 ratio [32]. Based on this, we hypothesize that miR-181c may promote gemcitabine resistance through the NDRG2/Mcl-1 axis. Let-7a suppresses expression of neurofibromatosis 2 (NF2) and enhances Stat3 phosphorylation and kinase activity, which lead to decreased apoptosis caused by gemcitabine and 5-FU treatment [33]. MiR-1249 was upregulated in gemcitabine-resistant and CD133+ CCA. It could modulate the chemotherapy-induced enrichment of CD+133 cells and thus contribute to gemcitabine resistance through frizzled class receptor 8 (FZD8), a negative regulator of the canonical Wnt pathway [34]. MiR-125a-5p was found to be up-regulated in CCA compared to corresponding normal tissue, potentially reducing sensitivity to gemcitabine. However, the literature does not discuss its mechanisms [35].

Several tumor suppressor miRNAs, including miR-29b, miR-205, miR-221, miR-637, let-7a, miR-424-5p, miR-520c-3p, miR-149-5p, and miR-328, have been identified as playing essential roles in gemcitabine resistance in CCA. Understanding the functions of these mechanisms reveals potential strategies for surmounting gemcitabine resistance in CCA. Several tumor suppressive miRNA contribute to gemcitabine resistance by modulation of apoptosis, including miR-29b, miR-221, and miR-637. MiR-29b and miR-221 could suppress phosphoinositide-3-Kinase regulatory subunit 1 (PIK3R1) expression, a PI3K pathway component, promoting apoptosis induced by gemcitabine in CCA [35]. Furthermore, targeting matrix metalloproteinase-2 (MMP-2), miR-29b, and miR-205 augments gemcitabine sensitivity in CCA. MMP-2 plays a role in cancer cell invasion and metastasis [35]. Overexpression of miR-637 heightens sensitivity to gemcitabine through inhibition of the LIM and SH3 protein 1 (LASP1), which plays a role in cancer progression and cytoskeleton organization [41]. Studies suggest that LASP1 may enhance CCA proliferation, invasion, and migration, while suppressing apoptosis. Thus, miR-637 might promotes gemcitabine sensitivity by improving apoptosis [40]. Up-regulated miR-205 has been observed to resensitize primary gemcitabine-resistant CCA cells to gemcitabine. Subsequent research revealed the role of MMP2 as the target of miR-205, involved in tumor microenvironment remodeling that contributes to gemcitabine resistance [35]. MiR-206 was found to be downregulated in intrahepatic cholangiocarcinoma (iCCA), affecting tumor proliferation, invasion, and migration. It is noteworthy that miR-206 expression in CCA decreased when co-cultured with normal fibroblast cells (NFs) which subsequently transformed into cancer-associated fibroblasts (CAFs). The CAFs potentially induced gemcitabine resistance and tumor deterioration. Moreover, the heightened expression of miR-206 in both iCCA and CAF possesses the capability to enhance sensitivity to gemcitabine, resulting in improved therapeutic outcomes [43]. MiR-424-5p, miR-520c-3p and miR-149-5p expression levels were downregulated in CCA. They had the potential to suppress both cancer stemness and EMT, thereby reversing the desensitization of CCA to gemcitabine. Increased miR-424-5p expression heightens gemcitabine sensitivity by blocking B-cell lymphoma 9 (BCL9) expression and activating the Wnt/β-Catenin signaling pathway [44]. MiR-520c-3p would restore CCA sensitivity to gemcitabine by suppressing MYCN [45]. This reduction in miR-149-5p' expression was found to significantly promote malignant biological behavior of CCA, mediated by the YAP1/TEAD2/SOX2 pathway [46]. Consequently, the upregulation of miR-149-5p could effectively restore CCA sensitivity to gemcitabine.

2.2. *miRNAs related 5-fluorouracil (5-FU) resistance*

5-FU is a common anti-metabolite drug utilized to treat numerous types of cancer, including CCA [47]. In advanced CCA, the combination of 5-FU and oxaliplatin has been used as a second-line therapy after progression on first-line cisplatin and gemcitabine, resulting in enhanced overall survival in comparison to solely managing active symptoms [48]. However, the effectiveness of 5-FU is often hindered by the development of general chemotherapy resistance. Several recent studies have revealed the role of miRNAs in mediating 5-FU resistance, with numerous miRNAs acting as potential modifiers of resistance by suppressing tumors.

MiR-20a-5p was up-regulated in CCA compared to corresponding normal tissue. It was found that overexpression of miR-20a-5p reverse 5-FU resistance induced by FALEC, a onco-lncRNA [49]. MiR-20a-5p could inhibit expression of SHOC, a gene of MAPK pathway, and *p*-ERK1/2, which might promote apoptosis induced by 5-FU [57]. MiR-320 and miR-204 function as a tumor suppressor in CCA. However, their expression is markedly decreased in CCA compared to adjacent normal bile duct tissue. Up-regulated miR-320 and miR-204 could facilitate apoptosis induced 5-FU by negatively regulated expression of Mcl-1 or Bcl-2 [50]. MiR-106b is noticeably downregulated in CCA and act as tumor suppressive miRNA. Recent studies indicate that it enhances 5-FU sensitivity in CCA by directing zinc finger and BTB domain-containing 7A (Zbtb7a), a transcriptional regulator involved in various cellular processes [51]. In colorectal cancer and osteosarcoma, inhibition of Zbtb7 may enhance tumor susceptibility to chemotherapeutic drugs by facilitating apoptosis [52,53]. Thus, it is speculated that miR-106 could override 5-FU resistance by modulating apoptosis. MiR-328 inhibits tumor proliferation and facilitates apoptosis induced by 5-FU by down-regulating GPAM [54]. Up-regulated miR-200 b/c exhibit the ability to hinder tumor migration and enhance the susceptibility of CCA cells to 5-FU treatment [55]. In CCA, miR-200 b/c plays a role in the expansion of CD133+ cells (cancer stem cells), thus leading to 5-FU resistance. However, miR-200b plays a contradictory role in CCA. As mentioned above, it could promote resistance to gemcitabine in CCA. MiR-885-5p exhibits tumor-suppressive effects in CCA, hindering tumor proliferation and metastasis [58]. Additionally, miR-885-5p may enhance the sensitivity of CCA cells to 5-FU by targeting myotrophin (MTPN), a protein associated with cell migration and invasion [56]. However, the mechanism underlying miR-885-5p-mediated resistance to 5-FU has yet to be elucidated.

2.3. *miRNAs related cisplatin-resistance*

Cisplatin is a coordination compound containing platinum that has widespread use in cancer treatment, particularly CCA [59]. The combination of cisplatin and gemcitabine is now considered the first-line standard of care for advanced CCA, demonstrating superior survival outcomes in comparison to gemcitabine monotherapy [48]. However, developing cisplatin resistance remains a crucial challenge in treating CCA. Several studies have illuminated miRNAs' role in cisplatin resistance in CCA.

MiR-199a-3p is a tumor suppressor miRNA associated with cisplatin resistance in various types of tumors, including CCA. Its role involves

regulating the mTOR signaling pathway by modulating Multidrug resistance gene 1 (MDR1), a multidrug resistance protein [61–63]. Upregulation of miR-199a-3p enhances CCA cell sensitivity to cisplatin by inhibiting MDR1 expression, thereby increasing its cytotoxic impact. The results demonstrate the potential of miR-199a-3p regulation in improving CCA chemotherapy [60]. MiR-637 has been linked to drug resistance in various types of cancer [64]. As mentioned above, miR-637 is significantly downregulated in CCA, and its decrease is linked to resistance to cisplatin via LASP1. MiR-637 might promotes cisplatin sensitivity by improving apoptosis [40]. MiR-520c-3p expression levels were downregulated in CCA. They had the potential to suppress both cancer stemness and EMT, thereby reversing the desensitization of CCA to cisplatin [45]. Upregulating miR-885-5p has demonstrated the capacity to overcome cisplatin resistance in cases of CCA. Its elevation of MTPN expression heightens cisplatin sensitivity, leading to the inhibition of tumor proliferation and metastasis [56]. However, the mechanism underlying miR-885-5p-mediated resistance to 5-FU has yet to be elucidated.

2.4. miRNAs related sorafenib-resistance

Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), has been shown to be effective in treating advanced hepatocellular carcinoma (HCC) by targeting pathways associated with angiogenesis and proliferation [65]. However, the efficacy of sorafenib in treating CCA is hindered by general resistance. A prospective study of unresectable and advanced CCA patients treated with sorafenib and best supportive care revealed a disease control rate (DCR) of 15.9 %, despite the absence of a control group for comparison [66]. In addition, patients with aberrant human organic cation transporter 1 (OCT1) variants that facilitate the intracellular accumulation of sorafenib exhibited heightened sensitivity to the drug in CCA [67]. In the context of sorafenib resistance in CCA, several studies have identified downregulation of tumor suppressor miRNAs as contributing factors. These miRNAs include miR-141, miR-330, and miR-138.

MiR-141 and miR-330 are acknowledged as tumor-suppressive miRNAs in cases of CCA. They possess the capability to hinder tumor proliferation and metastasis by regulating the Hippo pathway, which is a key mediator of organ size and cell growth [70,71]. MiR-141 and miR-330 can enhance the sensitivity of CCA cells towards sorafenib by precisely targeting the hOCT1 protein responsible for intracellular sorafenib accumulation [68]. On the contrary, miR-138 is a significant contributor to overcoming sorafenib resistance in CCA by modulation of tumor stemness. It targets the transcription factor Sex-determining region Y-related (SRY) high-mobility group box 4 (SOX4), which regulates tumor growth, metastasis, and stemness [69,72]. Downregulation of miR-138 is associated with increased proliferation, migration, and invasion in CCA [73].

3. lncRNAs and drug resistance

Long non-coding RNAs (lncRNAs) are RNA molecules exceeding 200 nucleotides and not coding for proteins. They possess significant roles in diverse cellular processes, such as regulating chromatin dynamics, gene expression, cell growth, differentiation, and development [74]. It have the ability to act as enhancer-like molecules, activate additional non-coding RNAs like miRNA and piRNA, as well as compete for RNA molecule binding [75]. Several lncRNAs have been identified as involved in drug resistance. These include HOTTIP, HOXD-AS1, LINC00665, NEAT-1, lncRNA H19, lnc-PKD2-2-3, and lncRNAMEG3, all of which have been implicated in drug resistance mechanisms. These processes include but are not limited to - cell proliferation, apoptosis, DNA repair, and drug efflux. Additionally, lncRNAs have the ability to interact with other molecules such as miRNAs and proteins and modify gene expression, thus managing cellular responses in context to drug exposure.

The expression of FALEC was significantly higher in 5-FU resistant CCA patients in comparison to normal control. It could sponge up miR-20a-5p and decrease its expression, thereby potentially enhancing resistance to 5-FU [49]. MiR-20a-5p could inhibit expression of SHOC, a gene of MAPK pathway, and *p*-ERK1/2, which might promote apoptosis induced by 5-FU [57]. Additionally, LINC01714 was significantly down-regulated in CCA and was observed to be correlated with a favorable prognosis. LINC01714 enhances sensitivity to gemcitabine by suppressing the phosphorylation of forkhead box O3 (FOXO3) [77]. Recent studies suggest that FOXP3 may play a role in chemo-resistance through its modulation of DNA damage repair [78]. Lnc-PKD2-2-3 and HOTTIP were found to be involved in resistance to chemotherapeutic agents by modulation of apoptosis. Lnc-PKD2-2-3 can sponge up miR-328, leading to increased expression of GPAM and restore 5-FU resistance [54]. HOTTIP can promote resistance to gemcitabine and cisplatin chemotherapy in CCA by regulating the miR-637/LASP1 pathway [41]. HOXD-AS1, LINC00665, and DLEU1 were discovered to contribute to resistance to chemotherapy by regulating the stemness of CCA. HOXD-AS1 function as a miR-520c-3p sponge, ultimately upregulating the expression of the MYCN, which contribute to gemcitabine-resistance [45]. LINC00665 promote gemcitabine resistance by acting as a sponge for miR-424-5p, leading to activation of the BCL9L/Wnt/β-Catenin pathway [44]. DLEU1 hinders stemness preservation in CCA and heightens susceptibility to gemcitabine by serving as a miR-149-5p sponge, ultimately leading to augmented YAP1 expression [46]. NEAT-1 has been linked to the promotion of gemcitabine resistance in CCA, although additional research is necessary to comprehend the exact mechanisms at play [79].

These findings illuminate the intricate regulatory functions of long non-coding RNAs in drug resistance and prognosis in CCA. Additional research is required to comprehend the fundamental mechanisms and assess their applicability as treatment targets.

4. Circ-RNAs and drug resistance

Indeed, circular RNAs (circRNAs) play a crucial role in multiple biological processes, including chemotherapy resistance in cancer. Various mechanisms have been suggested by which circRNAs can contribute to drug resistance in CCA [80]. Understanding the particular circular RNAs involved in drug resistance mechanisms in CCA and their functional roles will provide significant insights for developing new therapeutic strategies to conquer drug resistance and enhance patient outcomes.

Several circular RNAs have critically contributed to CCA, including cNFIB, SMARCA5, and HMGCS1-016. The evidence points to their significant involvement in the disease. Circular RNAs cNFIB is down-regulated in CCA, functions as a tumor suppressor [81]. Down-regulated cNFIB was significantly associated with aggressive characteristic and poor prognosis. High levels of cNFIB have been found to delay resistance to trametinib, a MEK inhibitor, by competitively interacting with MEK1, and thereby inhibiting the ERK signaling pathway. The expression of circ- SMARCA5 was reduced in CCA compared with normal tissue and associated with better prognosis [82]. It could restore CCA cell sensitivity to gemcitabine and cisplatin. Recent studies have indicated that SMARCA5 suppresses the expression of miR-95-3p, promoting apoptosis [85]. Perhaps SMARCA5 could overcome chemo-resistance by controlling apoptosis. HMGCS1-016 is a circ-RNA that is upregulated in CCA and is associated with adverse clinical outcomes [84]. It was found that HMGCS1-016 might suppress tumor-infiltrating $CD8^+$ T and contribute to suppressive tumor microenvironment via miR1236-3p/CD73 and GAL8. In CCA, patients with high-level of HMGCS1-016 benefit less from PD-1 antibody.

5. Discussion

Growing evidence suggests that non-coding RNAs, including

miRNAs, lncRNAs, and circRNAs, are involved in drug resistance mechanisms in CCA. Understanding the underlying mechanisms presents prospects to develop treatment plans aimed at subduing drug resistance in CCA. In summary, dysregulated ncRNAs in CCA, including miRNAs, lncRNAs, and circRNAs, have been found to contribute to drug resistance.

This is achieved through modulation of reduced drug uptake (MOC1-1a), enhanced drug export (MOC-1b), altered drug targets (MOC-3), enhanced DNA repair (MOC-4), pro-apoptotic (MOC-5a), pro-survival (MOC-5b), changes in the tumor microenvironment (MOC-6), and phenotypic transition (MOC-7). Therein, miR-141 and miR-330 promote CCA sensitivity to sorafenib by targeting hOCT1 for intracellular sorafenib accumulation. Furthermore, miR-21, miR199a-3p, and FALEC were upregulated in CCA and promoted drug export that conferred chemoresistance. Several dysregulated miRNAs may contribute to drug resistance in CCA by modulating apoptosis, including miR-200b, miR-210, miR-181c, let-7a, miR-221, miR637, miR-320, miR-204, miR-106b, and miR-328. In these miRNAs, down-regulated tumor suppressive miRNAs and up-regulated oncogenic miRNAs led to primary chemoresistance. Furthermore, the lncRNA lnc-PKD2-2-3, HOTTIP, and circular RNA SMARCA5 are downregulated in CCA, reflecting drug resistance via sponging miRNAs and inhibition of apoptosis induced by chemotherapeutic agents. In addition, several dysregulated ncRNAs would promote chemo-resistance by modulating of cancer stemness, including miR-1249, miR-149-5p, miR-424-5p, miR-520c-3p, miR-200 b/c, miR138, HOXD-AS1, LINC00665 and DLEU1. In summary, this study found that the dysregulated ncRNAs are involved in primary resistance to chemotherapy. Specifically, miR-130a-3p, miR-1249, miR-125a-5p, miR-29b, miR-221, miR-205, miR-424-5p, miR-20a-5p, miR-106b, miR-199a-3p, LINC00665, FALEC, and NEAT-1 were up-regulated in drug-resistant CCA cells compared to non-resistant CCA cells. These up-regulated ncRNAs are believed to contribute to secondary drug resistance in CCA. Interestingly, tumor derived extracellular vesicles could promote chemoresistance in CCA by delivering miR-210. Furthermore, dysregulated miRNAs developed drug resistance by modulating of interaction between CCA cell and tumor infiltrating immune cell. Up-regulated miR-206 in CAF and CCA cell override drug resistance. On the contrary, circHMGCS1 was negatively associated with tumor-infiltrating CD8+T cell that contributed to drug resistance in CCA. It is confusing that while we believe CCA cells with stemness traits tend to be more resistant to chemotherapy, the mechanisms of chemoresistance in cancer stem cells are still complex. Should we consider CCA stemness as a unique factor involved in chemo-resistance? It was reported that cancer stem cells develop resistance to chemotherapy by maintaining a high level of ABC transporter expression, enhancing DNA damage repair, and promoting angiogenesis [86]. Thus, we are still investigating whether dysregulated ncRNAs contribute to drug resistance by modulating the aforementioned mechanisms. The interaction between CCA and tumor-infiltrating immune cell was also promising aspect to override drug resistance. As is well-known, miRNA from chemo-resistant tumor-derived exosomes may confer resistance to chemotherapeutic agents in sensitive tumor cells. Similarly, the secretion of miRNA from CAFs is involved in the development of chemo-resistance [87]. It was reported that ncRNAs derived from chemo-resistance tumor or suppressive tumor-infiltrating immune cell developed drug resistance by modulating of apoptosis [88], ferroptosis [89], CSCs [90,91], and EMT [92]. Perhaps we can divide MOCs into two subgroups: “pre-effect” and “effect”. MOC-1 and MOC-2 belong to the “pre-effect” subgroup, where effective drug concentration is suppressed. MOC-3, MOC-4, and MOC-5 belong to the “effect” subgroup, where drug-induced DNA damage and apoptosis are inhibited and drug targets are altered. We believed that these dysregulated ncRNAs led to drug resistance by modulating of interaction between CCA and tumor-infiltrating immune cell (MOC-6) and CCA stemness (MOC-7). However, it is still necessary to consider the mechanisms of drug resistance in CCA that are involved in the tumor microenvironment and stemness of cancer.

Targeting dysregulated miRNAs in CCA represents one potential pathway to override chemo-resistance. Therapeutic interventions may involve designing strategies to induce miRNA-like function by introducing synthetic miRNA mimics or miRNA analogs that replicate the effects of tumor-suppressive miRNAs. It is also feasible to explore the restoration of tumor-suppressive miRNAs that have been down-regulated or the depletion of oncogenic miRNAs that have been up-regulated as potential therapeutic interventions [93]. RNA therapeutics currently were used including ASO [94], siRNA [95], shRNA [96], miRNA mimic [97], antimiRs [98], miRNA sponges [99], and miRNA masking ASOs [100]. The development of nanoparticle-based delivery systems has greatly enhanced the delivery of miRNA therapeutics and surmounted various restrictions of conventional delivery methods. In targeting miRNAs for therapeutic objectives, nanoparticles provide a number of benefits [101,102]. However, despite the increased interest and substantial research regarding lncRNAs and circRNAs, there are currently no lncRNA or circRNA-based therapeutics in clinical development for CCA or other illnesses. The translation of ncRNAs as therapeutic targets is still in its nascent phases, requiring further research and clinical trials to uncover their potential. In this review, we have highlighted the involvement of various non-coding RNAs, including miRNAs, lncRNAs, and circRNAs, in drug resistance in CCA. Understanding the underlying mechanisms by which these non-coding RNAs contribute to drug resistance can provide valuable insights for the development of novel therapeutic strategies in CCA. As our comprehension of the molecular mechanisms and biological functions of non-coding RNAs in CCA deepens, their clinical potential as therapeutic targets or diagnostic markers will likely be further investigated. Further research and precisely-designed clinical trials are vital in realizing the complete potency of miRNAs, lncRNAs, and circRNAs for optimizing prognosis and treatment outcomes in CCA patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

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CRediT authorship contribution statement

Zhaowei Wu: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shiming Jiang:** Supervision, Project administration, Investigation. **Yong Chen:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CCA	Cholangiocarcinoma
ncRNA	Non-coding RNA
lncRNA	Long non-coding RNA
circRNA	Circular RNA
snRNA	Small nuclear RNA
snoRNA	Small nucleolar RNA
MDR	Multiple drug resistance
CSC	Cancer stem cell
EMT	Epithelial-mesenchymal transition
MOC	Mechanism of chemoresistance
5-FU	5-fluorouracil
CDDP	cisplatin
PTEN	Phosphatase and Tensin Homolog
PTPN12	PTP non-receptor type 12
PPARα	Peroxisome Proliferator-Activated α-Receptor
FZD8	Frizzled 8
HIF-3α	Hypoxia-inducible factor-3α
NDRG2	N-myc downstream-regulated gene 2
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1
MMP-2	Matrix metalloproteinase-2
LASP1	LIM and SH3 protein 1
STAT3	Signal transducer and activator of transcription 3
BCL9	B-cell lymphoma 9
YAP1	Yes-associated protein1
GPAM	Glycerol-3-phosphate acyltransferase mitochondrial
MCL-1	Myeloid cell leukemia sequence 1
MTPN	Myotrophin
ZBTB7A	Zinc finger and BTB domain-containing 7A
mTOR	Mechanistic target of rapamycin
MDR-1	Multidrug resistance gene
OCT1	human organic cation transporter 1
SOX4	Sex-determining region Y-related (SRY) high-mobility group box 4
FOXO3	forkhead box O3

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