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Small but mighty: How microRNAs drive the deadly progression of cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma, also referred to as CCA, is a highly complex epithelial malignancy that can impact various organs and regions of the body, including the perihilar, intrahepatic, and distal organs. This cancer is characterized by the malignant growth of the epithelial lining in the bile ducts, which spans the entire biliary tree and is accountable for disease progression. The current state of affairs concerning CCA is concerning, with poor prognoses, high recurrence rates, and dismal long-term survival rates significantly burden healthcare facilities worldwide. Studies have identified numerous signaling pathways and molecules involved in the development and progression of CCA, including microRNAs, an important class of non-coding RNAs that have the ability to modulate these cellular signaling pathways significantly. In addition, microRNAs may serve as an innovative target for developing novel therapeutic approaches for CCA. In this review, we explore the underlying mechanisms and signaling pathways implicated in the initiation and progression of CCA, focusing on the future direction of utilizing microRNAs as a promising treatment option for this challenging malignancy.

1. Introduction

Cholangiocarcinoma (CCA), also called bile-duct cancer, is considered rare cancer with a poor prognosis originating from the biliary tree. Anatomically, CCA is classified into extra-hepatic (eCCA) and intra-hepatic (iCCA) types. iCCA is an aggressive primary liver malignancy with an increasing global incidence. iCCA develops within the liver parenchyma, whereas eCCA can arise anywhere along the extra-hepatic bile duct. eCCA are further subdivided into distal and perihilar subtypes. These subtypes may represent distinct molecular and epidemiologic properties [1,2]. A poor prognosis and short-term survival mostly distinguish CCA. Delay in diagnosis, absence of efficient treatment, and drug resistance are essential factors in CCA's poor prognosis. Radical surgical resection combined with lymphadenectomy is considered the only potentially curative treatment approach for CCA patients. Although radical surgical resection is the only curative approach, almost 70% of CCA cases are identified with unresectable or metastatic progressive cancer. Additionally, the vast majority of CCA patients are diagnosed at progressive stages of the disease, which are not candidates for surgical treatment. Gemcitabine, combined with cisplatin (GC), is considered the first-line chemotherapy in CCA patients who are not subjected to surgery [3,4].

Remarkable progress has been made in terms of identifying the functions of miRNAs and their role in cancer research as tumor suppressors or oncogenic biomarkers [5,6]. MicroRNAs (miRNAs) are small, single-stranded (19–25 nucleotides), non-coding RNAs that regulate

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gene expression by binding to sequence motifs located in 3′ untranslated regions (UTR) of mRNA transcripts [7,8]. It is demonstrated that miRNAs are ideal clinical biomarkers that can be isolated from plasma and serum and serve as diagnostic and prognostic tools during inflammation and tumorigenesis [9,10]. miRNAs are well-defined in the carcinogenesis of CCA by acting as an onco-suppressor or oncogene. The pivotal role of miRNAs in tumorigenesis and tumor suppressor functions are investigated in all the cancer features, including; tumor cell apoptosis, invasion and metastasis, proliferating signaling, and angiogenesis [11,12]. The purpose of this review is to outline the functions of miRNAs in the evolution of CCA. Also, we discussed miRNA's role in the pathogenesis of CCA, including its roles in proliferation and invasion, angiogenesis, immune escape, stemness, and autophagy. We also review their potential role as prognostic and diagnostic tools and their implication in therapeutic management.

2. Epidemiology and pathogenesis of CCA

CCA comprises approximately 3% of all gastrointestinal malignancies [13]. The median age of CCA diagnosis worldwide, particularly in Western countries, is about 70. CCA incidence varies geographically, with a substantially higher incidence in sections of Eastern countries than in the West. These variations in incidence reflect differences in genetic determinants. CCA affects both women and men, with a slight men preponderance [14]. Numerous studies have revealed the increasing incidence of iCCA. Britannia first described this; incidence and mortality rates increased by 15-fold for iCCA in 45 ages and above during 1968 – 1996. However, there was a steady reduction in eCCA during the same period. [15]. Further studies displayed the same results in increasing the incidence of iCCA and decreasing eCCA in many European nations, Australia, Japan, and the USA in both women and men [16]. Another study has reported the incidence of both iCCA and eCCA remained stable in France and Burgundy, but iCCA occurrence decreased in Denmark during recent decades [17,18]. Furthermore, data from the North American Association of Central Cancer Registries (NAACCR) reported that the incidence of iCCA reduced from 1998 to 2003, then its incidence increased between 2003 and 2009; the incidence of eCCA rose between 1998 and 2003 before plateauing from 2003 to 2009 [19]. Although the exact cause of CCA remained unknown, however, several known risk factors have been reported related to cholestasis and chronic biliary epithelium inflammation. These risk factors including primary sclerosing cholangitis (PSC) [20], infections by parasites [21], fibropolycystic liver diseases [22], Hepatitis [23], cirrhosis [24], metabolic disorders [25], chronic pancreatitis and inflammatory bowel disease (IBD) [26]. According to a cohort study with 1186 patients, sporadic cases of iCCA (0.5%) were reported in patients with Wilson's disease [27]. Among the mentioned risk factors, chronic inflammation or cholestasis is considered as a main risk factor leading to increased exposure of cholangiocytes to the inflammatory mediators, including TNF-α, IL-6, Wnt, and Cox2, which cause progressive mutations in tumor suppressor genes, proto-oncogenes, and DNA mismatch-repair (MMR) genes. In the state of cholestasis, an increase of bile acids leads to a reduction in pH, and induction of ERK1/2, Akt and NF-κB signaling pathways which induce cell growth, cell proliferation and migration. TGF-β, Hepatocyte Growth Factor (HGF), and Vascular Endothelial Growth Factor (VEGF) identified as other mediators with increased levels in cholangiocarcinoma [28].

2.1. microRNAs and CCA development

There is a class of non-coding RNAs known as microRNAs (miRNAs), and they have been linked to the regulation of cancer. This regulation includes the control of the cell cycle, apoptosis, metastasis, angiogenesis, autophagy, therapeutic resistance, and epithelial-mesenchymal transition, among other processes. Various microRNAs have been identified as dysregulated in CCA and associated with risk factors for CCA. This was established through recent research. There is growing evidence to show that changes in the expression of miRNAs may operate as oncogenic or suppressor miRNAs in the onset and development of colorectal cancer and that these changes may also act as useful biomarkers for clinical diagnosis and prediction of prognosis (Fig. 1). Below is the contribution of several miRNAs to CCA progression and pathogenesis.

2.2. Proliferation and invasion

Preliminary evidence by Meng et al. has reported that deregulated miRNA expression occurred in CCA and that miR-21 had a principal role in increasing cancer cell growth [29]. In a cohort study of primary CCA patients, increased expression of miR-21 and its oncogenic function was displayed by suppression of programmed cell death 4 (PDCD4) and tissue inhibitor of metalloproteinase 3 (TIMP3) targets [30]. Moreover, it is demonstrated that miR-26a had increased levels in human CCA tissues and CCA cell lines, and by activation β-catenin–dependent genes, miR-26a increased the proliferation of CCA cells [31]. It is interesting to note; the role of miR-26 as an onco-suppressor was found in hepatocellular carcinoma (HCC) [32]. In the subject of CCA cell proliferation, miR-181c and miR-191 act as tumor promoters to increase cancer cell growth [33]. In addition to oncogenic functions, miRNAs exhibit onco-suppressor properties by targeting mRNAs encoding genes, as well. miR-494, as a tumor suppressor biomarker, has reduced expression levels in CCA cells; it is shown that miR-494 impacts cell cycle regulation and cell cycle analyses confirmed that miR-494 leads to a significant G1/S checkpoint reinforcement [34]. It has been established that microRNAs can govern the transition from epithelial to mesenchymal cells.

The epithelial-mesenchymal transition (EMT) is a pathway that allows a polarized epithelial cell to undergo numerous biochemical changes. These changes ultimately lead to the adoption of properties that are characteristic of mesenchymal cells, including increased cell migration and invasion into stromal tissue as well as increased resistance to apoptosis. Evaluation of iCCA-specific miRNA profiles demonstrated that the signaling pathway linked miR-200c signaling to EMT was activated in iCCA samples with stem cell gene expression features. Reduced miR-200c led to activation EMT, while increased miR-200c levels resulted in reduced EMT and reduction of migratory ability and invasiveness of cancer cells [35]. miR-21 is essential for the proliferation of CCA cells and their metastasis; increased levels of miR-21 are related to reduced E-cadherin and elevated levels of vimentin (Vim) and N-cadherin (N-cad). miR-21 with induction EMT increases the invasion and migratory ability of CCA cancer cells [36]. Wan et al., in their study, have shown the oncogenic action of miR-383 by targeting Interferon Regulatory Factor 1 (IRF1) gene. IRF1 is a tumor suppressor that is active in CCA cells. It was shown that the levels of miRNA-383 in CCA samples were significantly higher than expected, and this miRNA is responsible for inducing proliferation, migration, and invasion in CCA tissue and cells via targeting IRF1 [37].

2.3. Angiogenesis

Angiogenesis plays an important role in tumor growth, maintenance, and metastasis. In CCA, studies reported that increased apelin and apelin receptor (APLNR) promotes angiogenesis and proliferation in CCA cells. Apelin stimulation also induced the expression of angiogenesis factors, including Ang and VEGF. Further analysis in this field demonstrated inhibition of the apelin/APLNR axis could inhibit CCA tumor growth in a xenograft model. anti-APLNR reduced angiogenesis and CCA cell growth by the reduction in vimentin, Ang, MMP-3, MMP-9, and VEGF in CCA cells [38]. Akirin2 is a key regulator of embryonic development. It has been shown, Akirin2 upregulation in CCA cells is associated with shorter overall survival (OS). In CCA, Akirin2, by targeting the IL-6/STAT3 pathway, induced overexpression of VEGF, which is important in the

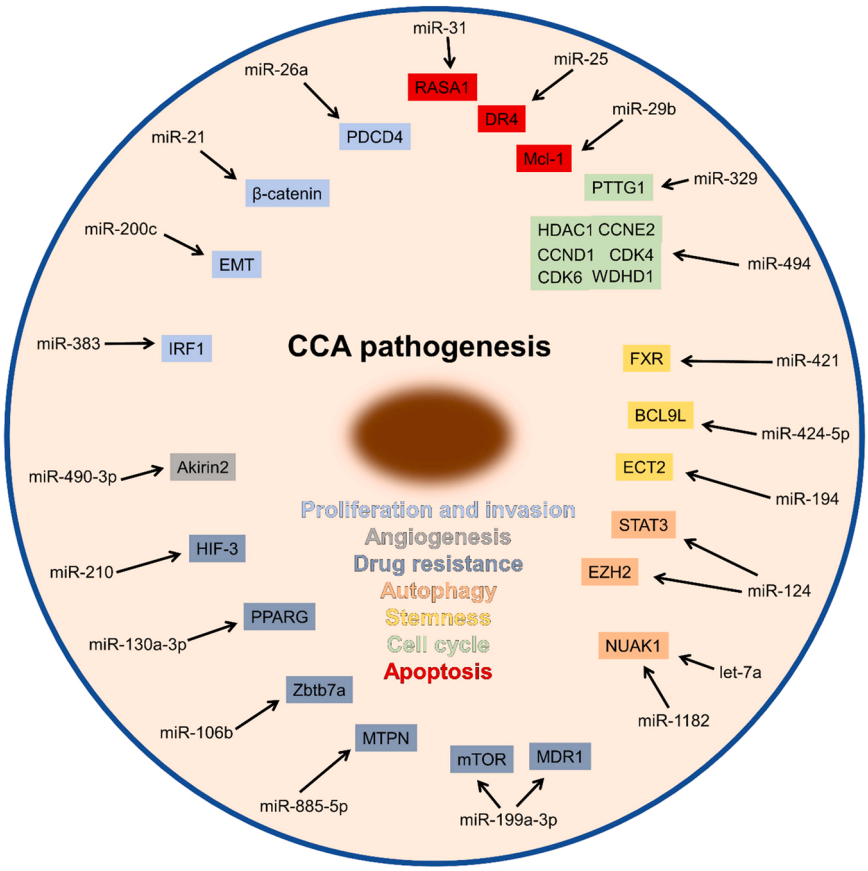

Fig. 1. The schematic overview of the involvement of miRNAs in CCA progression.

induction of angiogenesis. Moreover, Akirin2, by activating the EMT process, promoted the invasion and migratory ability of CCA cells. It is revealed that Akirin2 could be regulated by miR-490–3p at the post-transcriptional level and facilitate CCA cell progression via the IL-6/STAT3/VEGFA signaling pathway [39]. TGF-β is a multifunctional cytokine secreted by cancer cells or adjacent fibroblast cells. Receptors of this cytokine, TGFβR-I, and TGFβR-II, are strongly expressed by tumor cells. It is demonstrated that TGF-β1 can increase the expression of VEGF in cancer cells via autocrine or paracrine signaling and induce angiogenesis [40]. S100A8 (S100 calcium-binding protein A8) is highly expressed by cancer cells and regulates cancer cell progression. In CCA samples, S100A8 overexpression is associated with lymph node metastasis, differentiation, and the CCA patient's poor prognosis. S100A8 silencing attenuated the metastasis and migration of CCA cells [41].

2.4. Drug resistance

Drug resistance is a prevalent condition that reduces the efficacy of cancer therapies, including CCA. Regardless of the CCA subtype, a combination of gemcitabine and cisplatin is utilized as the first-line systemic therapy for some patients with advanced-stage CCA who are ineligible for surgical resection or liver transplantation [42]. Additionally, combinations of gemcitabine, cisplatin, and nab-paclitaxel [43], paclitaxel or 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan [44] are linked to increased patient survival. Genetic pathophysiology has received more attention in recent years, and carcinogenic and mutated genes have been found in numerous cancers, including CCA. This has sped up the creation of CCA-specific targeted therapies. Drug resistance, though, continues to be a major problem with such therapy. The function of miRNAs in CCA treatment resistance has been documented in a number of studies. As an example, miR-210 lowers the sensitivity of CCA cells to gemcitabine by inhibiting HIF-3 while maintaining HIF-1 activity [45]. Gemcitabine resistance was increased when the miR-130a-3p mimic was transfected into CCA cells, and PPARG was discovered to be a miR-130a-3p target gene [46]. In 5-FU resistant CCA cells, miR-106b expression was markedly downregulated. Instead, over-expression of miR-106b could inhibit Zbtb7a, re-sensitizing resistant CCA cells to 5-FU. Further evidence for miR-106b's possible significance as a prognostic marker in CCA comes from the correlation between lower expression of the gene and poor prognosis in CCA patients [47]. According to Wang et al., arsenic trioxide can increase the killing potential of 5-Fu and cisplatin while lowering the resistance of CCA cells to both drugs. Arsenic trioxide at low doses increased the expression of miR-885–5p, which had an anti-drug resistance impact. Combining sequencing findings with database predictions, it is identified that MTPN might be miR-885–5p's direct target. The sensitivity of CCA cells to 5-FU and cisplatin was improved after MTPN was knocked down. Their findings suggested that targeting the arsenic trioxide/miR-885–5p/MTPN axis could intensify the sensitivity of CCA cells to chemotherapy [48]. In CCA cell lines, it is revealed that miR-199a-3p expression is favorably linked with cisplatin sensitivity. By controlling the expression of mTOR, miR-199a-3p may improve the cisplatin sensitivity of CCA cell lines. Additionally, it has been suggested that miR-199a-3p overexpression may diminish the expression of MDR1 that is generated by cisplatin by reducing MDR1 synthesis and boosting MDR1 degradation, hence increasing the potency of cisplatin in CCA [49]. Furthermore, analysis of the miRNA expression profiles in CCA cells revealed a link between the expression levels of the miRNAs miR-29b, miR-205, and miR-221 and Gemcitabine resistance in HuH28 cells, indicating that ectopic overexpression of any of these miRNAs could reverse Gemcitabine resistance in these cells [50].

2.5. Autophagy

A multi-phase, homeostatic, self-degenerative cellular process called autophagy isolates dysfunctional, clustered, or mutated proteins as well as damaged organelles such as the mitochondria, peroxisomes, and endoplasmic reticulum into vesicles, which are then united with lysosomes to cause degeneration [51]. Autophagy appears to play both a stimulant and a suppressant role in the development of cancer. By interfering with autophagy processes, this particular ability has produced novel cancer therapy approaches [52]. CCA tissues and cells were found to have a high level of NUAK1 expression and a low level of miR-1182 and let-7a expression. NUAK1 has been identified as a target gene of microRNAs miR-1182 and let-7a. Significantly, overexpression of miR-1182 or let-7a triggered autophagy and suppressed cell proliferation [53]. Ma et al. examined the significance of miR-124 in CCA and observed that its expression was considerably downregulated in both patient tumor tissue and CCA cell lines. Their findings demonstrated that miR-124 induces autophagic flux in CCA cells. EZH2 and STAT3 have been identified as direct miR-124 targets [54].

2.6. Stemness

One of the main factors that predispose people to tumor aggressiveness, metastasis, and treatment resistance in cancer stemness. Tumorigenesis and cancer stemness can result from the dysregulation of miRNA biogenesis. In CCA stem cells, ECT2 was substantially expressed, whereas miR-194 was barely expressed, demonstrating the targeting relationship between the two genes. By inhibiting ECT2, Gao et al. showed that increased microRNA-194 reduces the stemness of cholangiocarcinoma cells through the Rho pathway [55]. When LINC00665 was silenced, sphere formation, migration, invasion, and the expression of EMT and stemness markers were decreased, while the gemcitabine-resistant CCA cells displayed higher EMT and stemness traits. Additionally, gemcitabine-resistant CCA cells increased Wnt/β-Catenin signaling, whereas LINC00665 knockdown inhibited this activation. The nucleus transcriptional regulator of Wnt/β-Catenin signaling, B-cell CLL/lymphoma 9-like (BCL9L), is essential for β-Catenin translocation to the nucleus and for promoting β-Catenin-dependent transcription. It was discovered that LINC00665 acted as a molecular sponge for miR-424–5p to control the expression of BCL9L. Furthermore, stemness and Wnt/β-Catenin activation were inhibited in resistant CCA cells when BCL9L was silenced, or miR-424–5p was overexpressed [56]. Ectopic expression of miR-421 increased colony formation and cell proliferation while drastically reducing the level of FXR protein in biliary tract cancer cells [57]. The expression of miR-137 was shown to be lower in CCA tissues when compared to nearby non-tumor tissues, according to a recent study. Additionally, it was found that CCA cell lines' expression of miR-137 was significantly lower than that of human intrahepatic biliary epithelial cells and that miR-137 overexpression inhibited CCA cell proliferation and reduced the capacity for colony formation [58].

2.7. Cell cycle

miRNAs are being looked into more and more as a potent group of gene modulators that are capable of playing significant roles in cellular processes, including the cell cycle. By negatively regulating WDHD1 and miR-494, which were elevated in CCA while miR-194 was down-regulated, miR-194 had an impact on the development of CCA. MiR-494 was found to inhibit EMT, cell viability, migration, invasion, and cell cycle progression when it was overexpressed [59]. Additionally, it has been observed that miR-494 therapy of CAA cancer cells restores the G1/S checkpoint by coordinating the down-regulation of CDK6, CDK4, CCND1, CCNE2, and HDAC1. This, in turn, causes a reduction in the phosphorylation of Rb and, ultimately, a delay in the cell cycle [34]. In biliary tract cancer, Zhong et al. discovered that the farnesoid X receptor is down-regulated while miR-421 is upregulated. miR-421 works as an oncogenic miRNA in cancer of the biliary tract. When miR-421 is inhibited, the cell cycle is arrested [57]. Through modulation of the PTTG1-mediated mitogen-activated protein kinase (MAPK) signaling pathway, miR-329 was predicted to influence CCA development. The targeting of PTTG1 by miR-329 inhibited the MAPK signaling pathway. MiR-329 overexpression and PTTG1 knockdown reduced CCA cell growth and triggered cell-cycle arrest [60]. To study the impact of miR-138/RhoC on cell viability and cell cycle distribution in CC, miR-138 mimics or miR-138 inhibitors were transfected into RBE and QBC939 CC cells. Compared to the control, transfection of RBE and QBC939 CC cells with miR-138 mimics dramatically lowered cell viability, whereas transfection with miR-138 inhibitor significantly boosted cell viability. Significantly more G1 phase cells were present in the miR-138 mimics group than in the miR-138 inhibitors group. The introduction of miR-138 mimics increased the G1/S ratio in RBE and QBC939 CC cells, but the suppression of miR-138 decreased this ratio [61]. Compared to control cells, overexpression of miR-191 was linked with a decrease in the proportion of cells in the G1/G0 phase and an increase in the proportion of cells in the S phase. In contrast to control cells, suppression of miR-191 expression raised the proportion of cells in the G1/G0 phase and decreased the proportion of cells in the S phase. These results indicate that miR-191 may boost cholangiocarcinoma cell proliferation by accelerating cell cycle progression [33].

2.8. Apoptosis

Several studies have looked at the role of miRNAs in the apoptotic process of CCA cells and how these short RNAs controlled this essential cancer feature. Mott et al. showed for the first time in 2007 that induced mir-29b expression lowered myeloid cell leukemia sequence 1 (Mcl-1) cellular protein levels and made CCA cells more susceptible to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) cytotoxicity. Transfection of non-malignant cells with a locked-nucleic acid antagonist of mir-29b boosted Mcl-1 levels and decreased TRAIL-mediated apoptosis. Mir-29 is, therefore, an endogenous regulator of Mcl-1 protein production and, as a result, apoptosis [62]. Furthermore, the discovery of the new miR-25 target TRAIL death receptor-4 (DR4) suggests a mechanism by which miR-25 aids in the avoidance of TRAIL-induced CCA apoptosis [63]. Hu et al. discovered that miR-31-mediated RASA1 downregulation increased cellular proliferation and prevented cellular apoptosis, in part by increasing the activity of the RAS-MAPK signaling pathway in CCA. In conclusion, the current investigation indicated that miR-31 and RASA1 play essential regulatory roles in CCA, implying that miR-31 and RASA1 might be viable diagnostic and/or therapeutic targets for CCA [64]. Upregulating miR-122 has been shown to inhibit bile duct cancer cell growth and cause apoptosis. MiR-122 might be exploited as a target for bile duct carcinoma therapy, offering cholangiocarcinoma patients a new therapeutic option [65]. Furthermore, restoring E2F2 in miR-365-overexpressing CCA cells increased cell viability and decreased cellular apoptosis. Overall, our findings highlighted the importance of miR-365 and its functional mechanism in CCA cells, providing fresh insight into the development of therapeutic targets for CCA therapy [66]. MiR-373 overexpression reduced the expression of ULK1, LC3, Beclin-1, and Bcl-2 while increasing the expression of P62, Bax, Caspase-3, and Caspase-9. In comparison to miR-373 overexpression alone, miR-373 mimic treatment, and subsequent ULK1 overexpression produced reverse regulation in the expression of these proteins. miR-373 targeted ULK1 to suppress autophagy and promote apoptosis in cholangiocarcinoma cells [67]. Furthermore, it has been revealed that miR-192–5p stimulates CCA cell proliferation while suppressing apoptosis via the MEK/ERK pathway, suggesting that it might be a possible therapeutic method for CCA therapy [68].

2.9. Prognosis and diagnosis ability

Numerous studies have suggested a large variety of biomarkers that can be found in tissue and molecules [69]. The deregulation of microRNA has been related to the development and progression of cancer, underlining the potential for these molecules to serve as important clinical prognostic markers. According to recent findings, these molecules play a significant part in both the beginning and the development of cancers that involve the biliary system. A microRNA dysregulation was seen in the biliary tract fluid obtained after ERCP. This microRNA dysregulation may be of clinical significance in patients diagnosed with CCA. A recent meta-analysis of microRNA profiling found that in CCA, 70 miRNAs had an upregulated expression level, whereas 48 miRNAs had a downregulated expression level [70]. Alterations in the expression of microRNA could potentially play oncogenic or suppressive roles in the development and progression of CCA, as well as serve as possible biomarkers for clinical diagnosis and prognosis prediction. These findings have been suggested by a number of studies [71]. Phosphatidylinositol-3 kinases/Akt, mitogen-activated protein kinase, and Ras pathways were the most prominently dysregulated [70].

A survival analysis of a 2013 research by Huang et al. revealed that CCA patients with greater expression levels of miRNA-21 had a worse prognosis (P0.05). Thus, miRNA-21 may play a significant role in cholangiocarcinoma invasion and metastasis, implying that miRNA-21 should be investigated further as a biomarker for cholangiocarcinoma prognosis [72]. Cheng et al. also discovered that a lower serum level of miR-106a is associated with a greater risk of lymph node metastasis [hazard ratio (HR) 18.3, 95% confidence interval (CI) 5.9–56.4, p 0.01]. Furthermore, lower levels of circulating miR-106a (HR 5.1; 95% CI 2.2–11.8; p 0.01) and non-radical surgery (HR 4.2; 95% CI 2.3–7.7; p 0.01) were independent indicators of poor outcome in CCA patients [73]. MiRNA-150 has been shown to be a non-invasive, sensitive blood biomarker for the diagnosis of CCA, especially when paired with Carbohydrate antigen 19–9 (CA 19–9) [74].

3. Therapeutic implication and future perspective

A promising new approach to the treatment of cancer is currently being developed using miRNA. The therapeutic applications of microRNAs function by either inhibiting overexpressed onco-miRNAs or replacing downregulated onco-suppressor-miRNAs [75]. Methodologically, anti-miRNA oligonucleotides (AMOs), anti-miRNA locked nucleic acid (LNA), anti-miRNA sponges, and genetic knockouts based on CRISPR/Cas9 genome-editing technologies were used to efficiently accomplish onco-miRNA silencing both in vitro and in vivo [75]. MiRNA replacement treatment, on the other hand, has frequently restored onco-suppressor-miRNA by injecting synthetically modified oligonucleotides (miRNA mimics) or viral vectors [75]. While promising, miRNA-based treatments have generated several concerns, including delivery, selectivity to particular target cells, degradation, and toxicity. The major tactics used to preserve miRNA against destruction are chemical modifications of nucleotides or the RNA backbone via methylation or LNAs, as well as the development of vehicles that encapsulate the RNAs. Furthermore, toxicity and side effects are possibly the most significant barriers to miRNA-based therapies [75]. Although viral and non-viral vectors have been created to boost delivery efficiency to target cells, their usage has been limited because of the danger of immunogenicity. Lipid- and polymer-based nanoparticles (NPs) have emerged as potential technological alternatives because of their effective transport and high safety profile [76]. MRX34, a formulation that is based on miR-34 mimics in liposomal particles, was the first method for restoring miRNA. This method was later used in clinical research that enrolled patients with solid malignancies, including hepatocellular carcinoma. Data from preliminary clinical trials demonstrated that MRX34 treatment has a high level of antitumor effectiveness as well as an outstanding safety profile [77]. Recent studies that demonstrated that the miR-34 mimic inhibited CCA cell development clearly suggested that miRNA-34-based treatment might be a potentially effective and safe therapeutic method in CCA [78]. These findings clearly suggested that miRNA-34-based treatment might be a potentially effective and safe therapeutic method in CCA. According to the findings of Li and colleagues, BDC cell proliferation, migration, and metastasis may all be inhibited by miR-195 being present in stroma-derived extracellular vesicles (EVs). In addition, the systemic delivery of EVs that were loaded with miR-195 prevented the growth of BDC tumors and increased the lifespan of animal models [79]. Xie et al. tested a novel treatment technique that is based on nanoparticles containing a cholesterol-modified polymeric antagonist of CXCR4 (C-X-C receptor type 4) and anti-miR-210. This treatment strategy was designed to combat the C-X-C receptor type 4 (CXCR4). They made this discovery after discovering that nanoparticles laded with CXCR4 antagonists and anti-miR-210 act synergistically to cause apoptosis and sensitize CCA cells to Gem/Cis treatment. They provided data that demonstrated that a novel nano-therapeutic method reduces tumor formation in CCA cell lines and animal models [80]. This technique combines reduction of CXCR4 and miR-210.

Author's contribution

All authors contributed to the study's conception and design. Conceptualization and searching were performed by Luay Ali Khaleel and Abduladheem Turki Jalil. The first draft of the manuscript was written by Luay Ali Khaleel and Rahman S. Zabibah. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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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