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The pivotal role of EMT-related noncoding RNAs regulatory axes in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) remains a major health problem worldwide, being the leading cause of cancer-related deaths, with limited treatment options, especially in its advanced stages. Tumor resistance is closely associated with the activation of the EMT phenomenon and its reversal, being modulated by different molecules, including noncoding RNAs (ncRNAs). Noncoding RNAs have the potential to function as both tumor suppressors and oncogenic molecules, controlling the malignant potential of HCC cells. Basically, these molecules circulate in the tumor microenvironment, encapsulated in exosomes. Their impact on cell biology is more significant than originally expected, which makes related research rather complex. The temporal and spatial expression patterns, precise roles and mechanisms of specific ncRNAs encapsulated in exosomes remain primarily unknown in different stages of the disease. This review aims to highlight the recent advances in ncRNAs related to EMT and classifies the described mechanism as direct and indirect, for a better summarization. Moreover, we provide an overview of current research on the role of ncRNAs in several drug resistance-related pathways, including the emergence of resistance to sorafenib, doxorubicin, cisplatin and paclitaxel therapy. Nevertheless, we comprehensively discuss the underlying regulatory mechanisms of exosomal ncRNAs in EMT-HCC via intercellular communication pathways.

KEYWORDS

hepatocellular carcinoma, noncoding RNA, epithelial-mesenchymal transition, chemoresistance, exosomes

1 Introduction

Hepatocellular carcinoma (HCC) is a common lethal malignancy among patients with chronic liver disease, with approximately 800,000 deaths annually, according to the GLOBOCAN 2020 report (Sung et al., 2021). Several treatment options are available for therapeutic purposes, such as trans-arterial chemoembolization (TACE) with anthracyclines, cisplatin, and multikinase inhibitor, sorafenib (Pratama et al., 2019). However, these treatments become challenging to manage, due to the appearance of invasion, metastasis and recurrence, whose key molecular sign is EMT (Yan et al., 2018).

EMT (epithelial-mesenchymal transition) is a morphogenetic process in which epithelial cells get a mesenchymal phenotype. In early EMT, transcriptional factors (TFs) are activated to repress epithelial genes and activate the mesenchymal ones. These transcriptional changes trigger the following key events: cell-cell junction dissociations, apical-basal polarity loss,

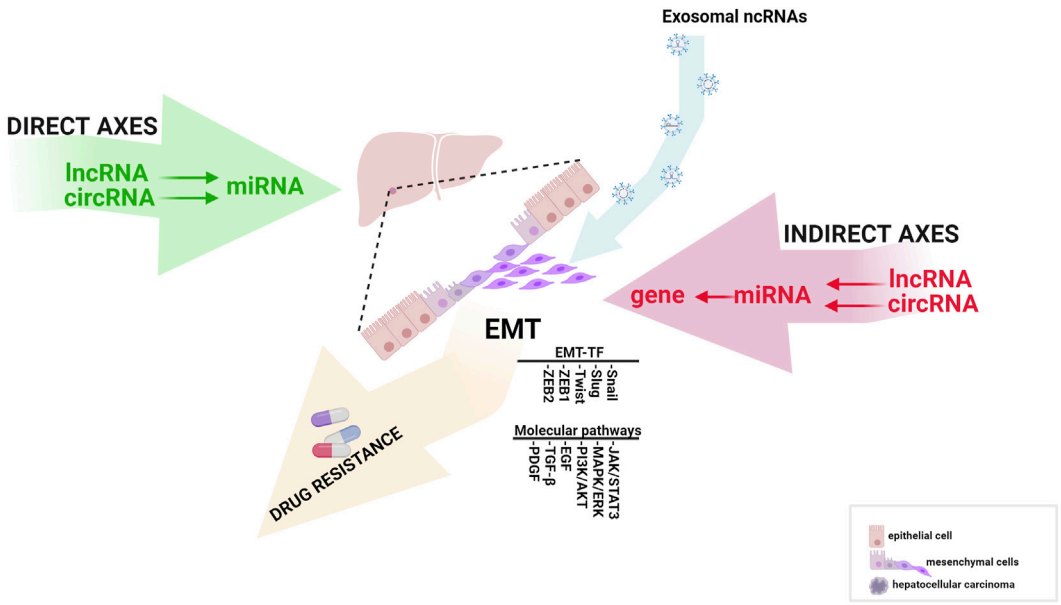

FIGURE 1
The influence of direct and indirect EMT-related ncRNA axes in HCC progression (created with biorender.com accessed on July 2023).

cytoskeleton architecture reorganization, the production of extracellular matrix (ECM) degradation enzymes, and cellular shape transformation. The activation of cellular pathways associates this process with proliferation, invasion, metastasis, and chemotherapy resistance (Yan et al., 2018; Dudas et al., 2020; Yang et al., 2020; Huang et al., 2022). Among these transformations, EMT is associated with numerous signaling pathways involved in inflammation, oncogenic and metabolic stress, hypoxia or apoptosis (Huang et al., 2022).

Moreover, many studies suggest that noncoding RNAs (ncRNAs), such as microRNAs (miRNAs), long-noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), have been linked to both the EMT process activation and inhibition. Indeed, these types of RNAs have multiple roles in cancerous cells because one ncRNA transcript could target many molecules involved in different signaling pathways (Toden et al., 2021; Khanbabaei et al., 2022).

This review highlights ncRNAs' significant direct and indirect signaling pathways in the EMT process and how these mechanisms are involved in HCC progression and chemoresistance. Finally, we provide an update on developing exosome-based therapies against HCC and their molecular aspects in EMT (Figure 1).

2 EMT-related ncRNAs mechanisms of action

As mentioned above, noncoding RNAs (ncRNAs), including microRNAs, lncRNAs and circRNAs, have oncogenic and tumor suppressor roles and regulate essential processes involved in cancer progression.

MicroRNAs (miRNAs) are noncoding single-stranded RNAs of approximately 22 nucleotides transcribed in pri-miRNA by RNA Pol II (Bartel, 2004). As described in the canonical pathway, Ribonuclease III and double-stranded-RNA-binding protein, DGCR8, recognize this structure in the nucleus, generating a pre-miRNA of ~65 nucleotides. Pre-miRNA is exported to the cytoplasm by an Exportin 5 and Ran-GTP complex and recognized by RNase III Dicer, which forms a miRNA duplex. This mature form is incorporated into an RNA-induced silencing complex (RISC), directing RISC to complementary mRNA targets (Cai et al., 2004). In brief, miRNAs function as negative regulators of genes when binding to RNA 3′-untranslated region (3′-UTR) (Ha and Kim, 2014). Besides that, the interaction with coding sequences, gene promoters, and 5′-UTR has been proved (O'Brien et al., 2018). Because each miRNA can regulate multiple targets containing specific miRNA response elements (MREs) (Bassett et al., 2014) and play a crucial role in a variety of molecular processes, they have been studied in all cancer types (Esquela-Kerscher and Slack, 2006; Volinia et al., 2006; Nicoloso et al., 2009). In HCC, miRNAs modulate cell cycle, proliferation, apoptosis, epithelial-mesenchymal transition and metastasis (Sidhu et al., 2015). Furthermore, our previous studies have shown that miRNAs are an important tool in the prognostic and diagnostic HCC (Mjelle et al., 2019; Sorop et al., 2020).

Long noncoding RNAs (lncRNAs) are transcripts of approximately 200 nucleotides, which usually RNA Pol II transcribes, but so do RNA Pol I and RNA Pol III (Statello et al., 2021; Mattick et al., 2023). Moreover, they have a wide diversity, with an average of 100,000 human lncRNAs (Mattick et al., 2023). At first, lncRNAs were defined as transcriptional "junk" or "noise." Still, in the past few years, more studies have shown the involvement of lncRNAs in different molecular pathways (Sun et al., 2017), indicating their interaction with DNA, RNA, or protein. The interaction mechanism could be: scaffold, decoy, guide, signal, or SINEUPs. Scaffold lncRNAs could act as archetype RNAs and are involved in the assembly of transcriptional regulators. The decoy

TABLE 1 Summary of ncRNAs direct signaling pathways and their action on HCC tumor cell processes.

ncRNA	Expression	Target	Axis pathway	ncRNA involvement in cellular process	References
miR-509-3p	↓	TWIST	miR-509-3p/TWIST/EMT	(−) EMT, (−) proliferation, (−) metastasis	Zhang et al. (2021)
miR-361-5p	↓	TWIST1	miR-361-5p/TWIST1/EMT	(−) EMT, (−) proliferation, (−) migration, (−) invasion	Yin et al. (2020)
miR-370-3p	↓	TWIST1, SNAIL	IL-8/STAT3/miR-370-3p/TWIST1, SNAIL/EMT	(−) EMT, (−) metastasis	Peng et al. (2022)
LINC00992	↑	miR-361-5p	LINC00992/miR-361-5p/TWIST1	(+) EMT, (+) proliferation, (+) metastasis, (+) invasiveness	Li et al. (2022)
LINC01133	↑	miR-199a-5p	LINC01133/miR-199a-5p/SNAIL; LINC01133/ANXA2/STAT3/cyclin D1	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Yin et al. (2021)
UCID	↑	miR-122, miR-203, miR-30b, miR-34a, miR-153	lnc-UCID/miR/SNAI1	(+) EMT, (+) metastasis, (+) migration, (+) invasion	Yuan et al. (2021)
circHIPK3	↑	miR-338-3p	circHIPK3/miR-338-3p/ZEB2	(+) EMT, (+) migration, (+) invasion, (+) metastases	Li et al. (2021)
circPTK2	↓	miR-92a	circPTK2/miR-92a/E-cadherin	(−) EMT, (−) proliferation, (−) invasion	Gong et al. (2020)

Note: downregulated expression (↓), upregulated expression (↑), inhibition of cellular process (−), enhance of cellular process (+).

mechanism implies acting as a competing endogenous RNA (ceRNA) or sponge of miRNAs, transcriptional factors, or RNA-binding proteins. In contrast, the guide mechanism involves the formation of a ribonucleoprotein complex, which targets a promoter or genomic loci (Rinn and Chang, 2012). Furthermore, lncRNAs could act as regulatory molecules (Nadhan et al., 2022) or SINEUPs containing SINE elements which enhance mRNAs translation (Toki et al., 2020).

Circular RNAs (circRNAs) are single-stranded RNAs with closed-loop structures and resistance to RNase R and exonucleases. They are generated from precursor RNA (pre-RNA) through back-splicing (Chen, 2016). This mechanism involves connecting a downstream donor site of a flanking downstream intron to an upstream acceptor site (Kristensen et al., 2019). Increasing research has revealed that circRNAs can sponge miRNAs, interact with proteins, interfere with transcription or splicing, or encode peptides (Zhang and Wang, 2021).

EMT plays a pivotal role in the early stage of metastasis (Bakir et al., 2020); thus, many studies have been conducted to determine the function of ncRNAs in this highly dynamic phenomenon. Therefore, this review underlines two types of mechanisms: direct and indirect.

2.1 Direct EMT-related ncRNAs' mechanism of action

Direct mechanism involves direct interaction between miRNA and EMT-regulatory factors, such as twist family bHLH transcription factor 1 (TWIST), snail family transcriptional repressor 1 (SNAIL), or zinc finger E-box binding homeobox 1/2 (ZEB1/2) (Skovierova et al., 2018). We defined this mechanism by three crucial axes: miRNA/EMT, lncRNA/miRNA/EMT, and circRNA/miRNA/EMT.

Several miRNAs, such as miR-509-3p (Zhang et al., 2021), miR-361-5p (Yin et al., 2020), and miR-370-3p (Peng et al., 2022), have been found to inhibit TWIST1 expression via targeting its 3′UTR and to abate the EMT process. Li et al. (2022) observe that LINC00992 downregulates miR-361-5p and upregulates TWIST1, thus promoting cell proliferation, migration, and invasion. In addition, miR-370-3p decreases TWIST1 and SNAIL, affecting interleukin 8 (IL-8) expression and restraining the metastasis capacity in HCC cells (Peng et al., 2022). In contrast, LINC01133 (Yin et al., 2021) and lnc-UCID (Yuan et al., 2021) increase EMT by acting as a sponge of miRNAs, increasing SNAIL expression. Furthermore, circHIPK3 promotes metastases and ZEB2 expression via inhibiting miR-338-3p (Li et al., 2021). In contrast, circPTK2 and E-cadherin compete for binding miR-92a that, aggravates proliferation and invasion, while circPTK2 suppresses miRNA's effect in HCC cells (Gong et al., 2020), as summarized in the direct mechanism part from Table 1.

2.2 Indirect EMT-related ncRNAs' mechanism of action

The indirect mechanism involves miRNA/mRNA, lncRNA/miR/mRNA, and circRNA/miRNA/mRNA regulatory axes that modulate an EMT molecule.

2.2.1 miRNA/mRNA axes

Numerous miRNA/mRNA axes have been found to be involved in the EMT process (Table 2).

For instance, Shen et al. (2021) have found that miRNA-10a-5p is downregulated in HCC tissues and decreases EMT in HCC cells by targeting spindle and kinetochore-associated complex subunit 1 (SKA1). SKA1 is upregulated in tumors, promoting cancer progression, and has a prognostic value in HCC (Chen et al.,

TABLE 2 Summary of miRNAs signaling pathways and their action on HCC tumor cell processes.

miRNA	Expression	Target	Axis pathway	miRNA involvement in cellular process	References
miR-10a-5p	↓	SKA1	miR-10a-5p/SKA1	(–) EMT, (–) migration, (–) invasion, (–) tumor formation *in vivo*	Shen et al. (2021)
miR-143-3p	↓	FGF1	miR-143-3p/FGF1/EMT	(–) EMT, (–) proliferation, (–) invasion	Peng et al. (2021)
miR-139-5p	↓	WTAP	miR-139-5p/WTAP/EMT	(–) EMT, (–) invasion, (–) proliferation	Liu et al. (2021)
miR-181 a/b/c/d	↑	CDX2, GATA6, NLK1	miR-181/CDX2, GATA6, NLK1	(+) stemness	Ji et al. (2009)
miR-181b	↑	TIMP3	miR-181b/TIMP3/TGF- β	(+) migration, (+) invasion, (+) tumor formation *ex vivo*	Wang et al. (2010)
miR-181a	↑	BIM	mir-181a/TGF- β/EMT	(+) EMT	Brockhausen et al. (2015)
miR-181ab1	↑	CBX7	mir-181/TGF- β/EMT	(+) EMT, (+) proliferation	Chen et al. (2022)
miR-23b-3p	↓	c-MET	miR-23b-3p/c-MET/TGF-β1/EMT	(–) EMT, (–) migration, (–) invasion	Park et al. (2022)
miR-4521	↓	FAM129A	miR-4521/FAM129A/EMT	(–) EMT, (–) migration, (–) proliferation, (+) apoptosis	Ayesha et al. (2022)
miR-7	↓	BCL2L1	miR-7/BCL2L1/P53/EMT	(–) EMT, (–) proliferation, (–) metastasis	Zhang et al. (2023)
miR-22-3p	↓	SPRY2	miR-22-3p/CBL/SPRY2/ERK/EMT	(–) EMT, (–) migration, (–) invasion, (–) Cancer stem cell features	Zeng et al. (2020); Cui et al. (2023)
miR-383	↓	RBM3	miR-383/RBM3/STAT3/EMT	(–) EMT	Zhang et al. (2022)

Note: downregulated expression (↓), upregulated expression (↑), inhibition of cellular process (–), enhance of cellular process (+).

2018; Song et al., 2022). Other oncosuppressors are miR-143-3p and miR-139-5p, which repress fibroblast growth factor 1 (FGF1) and Wilms' tumor 1-associating protein (WTAP). Those proteins increase EMT, proliferation and invasion of HCC cells (Liu et al., 2021; Peng et al., 2021). Moreover, Zhu et al. (2021) declare that miR-139-5p is regulated by lncRNA TTN antisense RNA 1 (TTN-AS1) and inhibits Sparc/osteonectin, cwcv, and kazal-like domains proteoglycan 1 (SPOCK1), an oncogenic proteoglycan involved in EMT (Vancza et al., 2022).

Growing studies have supported the importance of transforming growth factor beta (TGF-β) in HCC via SMAD/non-SMAD-dependent signaling pathways, which induce EMT-TFs (Hao et al., 2019). Several studies have shown that the miR-181 family positively correlates with TGF-β pathways, thus increasing EMT, tumor progression and stemness (Ji et al., 2009; Wang et al., 2010; Brockhausen et al., 2015; Chen et al., 2022). In contrast, miR-23b-3p has been proven to inhibit TGF- β1-induced EMT and block invasion and migration (Park et al., 2022).

Apoptosis or programmed cell death is a complex mechanism that involves death receptors (extrinsec pathway) and mitochondria (intrinsic pathway), by which it maintains cell homeostasis (Schattenberg et al., 2011). As discussed above, EMT confers resistance to apoptosis (Valdes et al., 2002). Interestingly, miR-4521 acts as an oncosuppressor in HCC cells by modulating mechanisms involved in proliferation and apoptosis. On the one hand, miR-4521 activates two apoptosis pathways (p-FAK/p-Akt/MDM2/P53 and FAK/p-Akt/BCL-2/BAX/Cytochrome-C/Caspase-3/Caspase-9) by decreasing the expression of family with sequence similarity 129 member A (FAM129A); on the other hand, it thereby attenuates invasivity by blocking TIMP-1/MMP9/MMP2, p-FAK/p-Akt and EMT pathways (Ayesha et al., 2022).

Moreover, the miR-7/BCL2L1/P53 and miR-22-3p/CBL/SPRY2/ERK axes decrease EMT, invasion, proliferation and migration (Cui et al., 2023; Zhang et al., 2023). Another EMT inhibitor is miR-383, which negatively regulates the multi-functional RNA-binding protein (RBM3) expression. As reported, RBM3 upregulates signal transducer and activator of transcription 3 (STAT3) expression via binding to its mRNA (Zhang et al., 2022). In addition, STAT3 targets the TWIST promoter and positively regulates its transcriptional activity in HCC cells, thus inducing EMT (Zhang et al., 2015).

Moreover, many studies highlight indirect mechanisms that imply lncRNA/miRNA/mRNA and circRNA/miRNA/mRNA axes.

2.2.2 lncRNA/miRNA/mRNA axes

Table 3 shows the lncRNA/miRNA/mRNA axes related to EMT in HCC. According to their oncological role, lncRNAs could be classified into two groups: onco-suppressor and oncotargets. Therefore, within the last 3 years, five lncRNAs, TMEM220-AS1 (Cao et al., 2021), lncRNA miR503HG (Song and Qiu, 2021), LINC02362 (Li et al., 2022), LINC02027 (Wang et al., 2023) and SATB2-AS1 (Huang et al., 2023), have been documented to function as miRNA sponge, to decrease a gene that promotes the EMT process. For instance, Huang et al. (2023) show that SATB2-AS1 is observably reduced in HCC tissues compared to adjacent tissues and its overexpression hampers tumor growth and metastasis *in vitro*. Besides, SATB2-AS1 also acts as a ceRNA for miR-3678-3p. This miRNA accelerates cell proliferation and suppresses cell apoptosis by blocking GRIM-19 (gene associated with retinoic-interferon-induced mortality 19), a negative STAT3/HIF-1α pathway regulator (Huang et al., 2023).

TABLE 3 Summary of lncRNAs signaling pathways and their influence in HCC tumor cells processes.

lncRNA	Expression	Target	Axis pathway	lncRNA involvement in cellular process	References
TMEM220-AS1	↓	miR-484	lnc-TMEM220-AS1/miR-484/MAGI1	(−) EMT, (−) proliferation, (−) invasion, (−) metastasis, (−) tumor growth, (+) apoptosis	Cao et al. (2021)
miR503HG	↓	miR-15b	lncRNA miR503HG/miR-15b/PDCD4	(−) EMT, (−) angiogenesis, (−) migration, (−) invasion	Song and Qiu (2021)
LINC02362	↓	miR-516b-5p	LINC02362/miR-516b-5p/SOCS2	(−) EMT, (−) proliferation, (−) migration, (−) invasion, (+) apoptosis	Li et al. (2022)
LINC02027	↓	miR-625-3p	LINC02027/miR-625-3p/PDLIM5	(−) EMT, (−) proliferation, (−) migration, (−) invasion	Wang et al. (2023)
SATB2-AS1	↓	miR-3678-3p	lnc-SATB2-AS/miR-3678-3p/GRIM-19/STAT3/HIF-1α	(−) EMT, (−) proliferation, (−) invasion, (−) migration, (−) metastasis, (−) tumor growth, (+) apoptosis	Huang et al. (2023)
LINC00668	↑	miR-532-5p	LINC00668/miR-532-5p/YY1	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Xuan et al. (2020)
LINC00922	↑	miR-424-5p	LINC00922/miR-424-5p/ARK5	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Ye et al. (2021)
UNC5B-AS1	↑	miR-4306	UNC5B-AS1/miR-4306/KDM2A	(+) EMT, (+) proliferation, (+) migration	Huang et al. (2021)
BACE1-AS	↑	miR-377-3p	lnc-BACE1-AS/miR-377-3p/CELF1	(+) EMT, (+) invasion, (+) migration, (+) metastasis	Liu et al. (2021)
DUXAP8	↑	miR-9-3p	lnc-DUXAP8/miR-9-3p/IGF1R	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Guan et al. (2021)
LOC554202	↑	miR-485-5p	LOC554202/miR-485-5p/BSG	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Yang et al. (2022)
SNHG1	↑	miRNA-376a	lnc-SNHG1/miR-376a/FOXK1/SNAIL	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (−) apoptosis	Meng et al. (2021)
HAGLROS	↑	miR-26b-5p	lnc-HAGLROS/miR-26b-5p/KPNA2/p53	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (−) apoptosis	Tang et al. (2022)
DARS-AS1	↑	miR-3200-5p	lnc-DARS-AS1/miR- 3200-5p/CKAP2/FAK/ERK	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) cell growth, (+) metastasis, (−) apoptosis	Feng et al. (2021)
SNHG12	↑	miR-516a-5p	lnc-SNHG12/miR-516a-5p/HEG1	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (−) apoptosis	Chen et al. (2021)
PRR34-AS1	↑	miR-296-5p	lnc-PRR34-AS1/miR-296-5p/E2F2/SOX12/Wnt/beta-catenin	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) tumor growth	Qin et al. (2021)
NUTM2A-AS1	↑	miR-186-5p	lnc-NUTM2A-AS1/mIR-186-5p/KLF7/Wnt/beta-catenin	(+) EMT, (+) invasion, (+) cell growth, (+) stemness, (−) apoptosis	Long et al. (2023)
LINC01278	↑	miR-1258	β-catenin/TCF-4/LINC01278/miR-1258/SMAD2/3	(+) EMT, (+) invasion, (+) migration, (+) metastasis	Huang et al. (2020)
CRNDE	↑	miR-539-5p	lnc-CRNDE/miR-539-5p/POU2F1/AKT/NF-kB	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Li et al. (2020)
HCP5	↑	miR-29b-3p	lnc-HCP5/miR-29b-3p/DNMT3A/AKT	(+) EMT, (+) invasion, (+) cell growth, (+) metastasis, (−) apoptosis	Zhou et al. (2021)
KDM4A-AS1	↑	miR-411-5p	lnc-KDM4A-AS1/miR-411-5p/KPNA2/AKT/HIF-1α	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) metastasis, (+) tumor growth	Chen et al. (2021)
MAPKAPK5-AS1	↑	miR-154-5p	lnc-MAPKAPK5-AS1/miR-154-5p/PLAGL2/EGRT/AKT/HIF-1α	(−) EMT, (−) proliferation, (+) apoptosis, (−) metastasis	Wang et al. (2021)
TTN-AS1	↑	miR-139-5p	lnc-TTN-AS1/miR-139-5p/SPOCK1	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) metastasis, (+) tumor growth, (−) apoptosis	Zhu et al. (2021)

Note: downregulated expression (↓), upregulated expression (↑), inhibition of cellular process (−), enhance of cellular process (+).

On the other hand, several lncRNAs increase EMT by sponging miRNAs that target oncogenes. LncRNAs such as LINC00668 (Xuan et al., 2020), LINC00922 (Ye et al., 2021), UNC5B-AS1 (Huang et al., 2021), BACE1-AS (Liu et al., 2021), DUXAP8 (Guan et al., 2021) and LOC554202 (Yang et al., 2022) were upregulated in HCC to contribute to specific lncRNA/miR/mRNA axes induced EMT. SNHG1 is another lncRNA with high expression levels in HCC; it is negatively correlated to a poor patient prognosis.

TABLE 4 Summary of circRNAs signaling pathways and their influence in HCC tumor cells processes.

circRNA	Expression	Target	Axis pathway	circRNA involvement in cellular process	References
circFGGY	↓	miR-545-3p	circFGGY/miR-545-3p/SMAD7	(−) EMT, (−) invasion, (−) migration, (−) cell growth	Feng et al. (2022)
circ_0000098	↓	miR-1204	circ_0000098/miR- 1204/ALX4	(−) EMT, (−) proliferation, (−) migration, (−) invasion	Li et al. (2021)
circEPB41L2	↓	miR-590-5p	circEPB41L2/miR-590-5p	(−) EMT, (−) proliferation, (−) migration, (−) invasion, (−) metastasis	Chen et al. (2021)
circ_0004913	↓	miR-184	circ_0004913/miR-184/HAMP	(−) EMT, (−) proliferation, (−) migration, (−) invasion, (−) tumor growth	Wu et al. (2020)
circ_0003998	↑	miR-143-3p	circ_0003998/miR-143 -3p/FOSL2; circ_0003998/miR-143 -3p/PCBP1/CD44v6	(+) EMT, (+) migration	Song et al. (2020)
circ_0101145	↑	miR-548c-3p	circ_0101145/miR-548c-3p/LAMC2	(+) EMT, (+) proliferation, (+) migration, (+) metastasis	Jin et al. (2020)
circBACH1	↑	miR-656-3p	circBACH1/miR-656-3p/SERB1	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) tumor growth, (−) apoptosis	Li et al. (2021)
circPUM1	↑	miR-1208	circPUM1/miR-1208/MAP3K2	(+) EMT, (+) migration, (+) invasion	Zhang et al. (2021)
circ_0051040	↑	miR-569	circ_0051040/miR-569/ITGAV	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) tumor growth, (+) metastasis	Ju et al. (2022)
circ_0001459	↑	miR-6165	circ_0001459/miR-6165/IGF1R	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) tumor growth, (+) metastasis	Shen et al. (2022)
circSEC24A	↑	miR-421	circSEC24A/miR-421/MMP3	(+) EMT, (+) proliferation, (+) invasion, (+) migration, (+) cell growth	Zhang and Zhou (2022)
		miR-455-3p	circSEC24A/miR-455-3p/PPM1F	(+) EMT, (+) proliferation, (+) invasion, (+) metastasis, (+) tumor growth, (−) apoptosis	Liao et al. (2021)
circ_0003288	↑	miR-145	circ_0003288/miR-145/PD-L1	(+) EMT, (+) migration, (+) invasion	Xu et al. (2021)
circ_0091579	↑	miR-136- 5p	circ_0091579/miR-136-5p/TRIM27	(+) EMT, (+) proliferation, (+) migration, (+) invasion, (+) cell cycle progression	Mao et al. (2022)
circTOLLIP	↑	miR-516a-5p	circTOLLIP/miR-516a-5p/PBX3/EMT	(+) EMT, (+) proliferation, (+) metastasis	Liu et al. (2022)
circCDR1as	↑	miR-1287	circCDR1as/miR-1287/Raf1 and MEK/ERK	(+) EMT, (+) proliferation, (+) metastasis	Zhang et al. (2020)
circ-TLK1	↑	miR-138-5p	circTLK1/miR-138-5p	(+) EMT, (+) proliferation, (+) migration, (+) invasion	Lu et al. (2022)
circFoxo3	↑	miR-199a-5p	circFoxo3/miR-199a-5p/ABCC1	(+) EMT, (+) invasion, (+) tumor growth	Huang et al. (2020)

Note: downregulated expression (↓), upregulated expression (↑), inhibition of cellular process (−), enhance of cellular process (+).

SNHG1 regulates cell proliferation and invasion via EMT through miR-376a binding to elevate forkhead box protein K1 (FOXK1) expression, a molecule that binds and upregulates SNAIL (Meng et al., 2021). HAGLROS knockdown impaired HCC tumorigenesis *in vitro* and *in vivo*. HALGROS increases the karyopherin α2 (KPNA2) level and suppresses p53 signaling to abate apoptosis by acting as a miR-26b-5p sponge (Tang et al., 2022). DARS-AS1 induces EMT via interacting with miR-3200-5p, further promoting Cytoskeleton associated protein 2 (CKAP2) expression and FAK/ERK pathway activation (Feng et al., 2021).

SNHG12 (Chen et al., 2021), PRR34-AS1 (Qin et al., 2021) and NUTM2A-AS1 (Long et al., 2023) axes induce EMT via Wnt/β-catenin signaling. Furthermore, Huang et al. (2020) point out that miR-1258 is downregulated in HCC patients. *In vivo,* experiments showed that the miR-1258 overexpression in nude mice impeded metastatic lung nodule formation. At the molecular level, LINC01278 acts as a sponge of miR-1258 and upregulates SMAD2/3, thus suppressing E-cadherin and enhancing vimentin expression. Moreover, transcription factor 4 (TCF-4) binds to the promoter site of LINC01278 and increases β-catenin expression, TGF-β and Wnt/β-catenin pathways, thereby activating the LINC01278/miR-1258/Samd2/Smad3 axis (Huang et al., 2020).

CRNDE and HCP5 induce Akt pathway activation by sponging miR-539-5p andmiR-29b-3p, respectively, to promote the EMT and the progression of HCC (Li et al., 2020; Zhou et al., 2021). Furthermore, two others oncogenic lncRNAs, KDM4A-AS1 and MAPKAPK5-AS1, activated by hypoxia-inducible factor 1-alpha (HIF1α), have also been found to increase protein kinase B (Akt) (Chen et al., 2021; Wang et al., 2021); their corresponding axes being listed in Table 3.

2.2.3 circRNA/miRNA/mRNA axes

In the Table 4 there are highlighted critical pathways that involve circRNAs. In HCC, the levels of circFGGY (circ_0006633) (Feng et al., 2022), circ_0000098 (Li et al., 2021), and circEPB41L2 (Chen et al., 2021) are downregulated in tumor tissues and inhibit EMT, proliferation, migration, and invasion. In summary, authors highlight circFGGY/miR-545-3p/Smad7 (Feng et al., 2022), circ_0000098/miR-1204/ALX4 (Li et al., 2021) and circEPB41L2/miR-590-5p (Chen et al., 2021) axes as being important in HCC. Furthermore, Wu et al. (2020) revealed that circ_0004913 was downregulated in HCC tissues and that the overexpression of circ_0004913 constrained proliferation, EMT and metastasis by acting as a sponge of miR-184 and promoting hepcidin antimicrobial peptide (HAMP) expression. In brief, the circ_0004913/miR-184/HAMP axis regulates JAK2/STAT3/Akt signaling in HCC cells (Wu et al., 2020).

In contrast, six circRNAs, circ_0003998 (Song et al., 2020), circ_0101145 (Jin et al., 2020), circBACH1 (Li et al., 2021), circPUM1 (Zhang et al., 2021), circ_0051040 (Ju et al., 2022) and circ_0001459 (Shen et al., 2022), have been observed to manipulate various miR/mRNA axes to induce EMT. Besides, elevated level of circSEC24A leads to the expression of protein phosphatase, Mg2+/Mn2+ dependent 1F (PPM1F) and matrix metalloproteinase 3 (MMP3) by sponging miR-455-3p and miR-421, respectively (Liao et al., 2021; Zhang and Zhou, 2022). MMPs are a class of enzymes that degrade extracellular matrix (ECM) proteins (Klein and Bischoff, 2011). In HCC, it was reported that MMP3 promotes EMT and metastasis (Scheau et al., 2019).

Circ_0003288 is an oncogenic RNA that enhances EMT by increasing programmed death-ligand 1 (PD-L1) and Akt pathways via miR-145 sponging (Xu et al., 2021). Circ_0091579 has been demonstrated to pin HCC patients and its downregulation inhibits EMT and promotes apoptosis *in vitro*. Also, miR-136-5p is a direct target of circ_0091579 and its overexpression suppresses the malignant potential of HCC cells via regulating tripartite motif containing 27 (TRIM27) expression (Mao et al., 2022).

Moreover, the Toll interacting protein (TOLLIP)-derived circRNA (circTOLLIP) is also found to be involved in the EMT of HCC. CircTOLLIP is upregulated in HCC via eukaryotic translation initiation factor 4A3 (EIF4A3), an RNA-binding protein. This circRNA acts as a ceRNA for miR-516a-5p, thus upregulating PBX3 and exhibiting pro-tumor roles *in vitro* and *in vivo* (Liu et al., 2022).

CircRNA CDR1as is highly expressed in some cancers (Jiang et al., 2020). Specifically, circRNA CDR1as is overexpressed in HCC tissues and its expression positively regulates EMT, proliferation and metastasis in HCC cells via the miR-1287 sponge. This circRNA enhances Raf-1 proto-oncogene, serine/threonine kinase (RAF1) expression, a crucial molecule in the RAS/RAF/MEK/ERK pathway (Zhang et al., 2020).

3 The role of ncRNA/mRNA axes in HCC drug resistance

As discussed above, EMT is associated with chemotherapy resistance by avoiding cell death mechanisms (De Las Rivas et al., 2021). Therefore, a growing number of studies have supported the importance of EMT-related ncRNAs in molecular pathways of different therapies (He et al., 2022).

Sorafenib is the first-line FDA-approved treatment for HCC (Niu et al., 2021) and an oral multikinase inhibitor that targets vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), hepatocyte factor receptor (KIT), or other molecules to decrease angiogenesis. HCC cells acquire resistance to sorafenib by different molecular pathways, including EMT (Marisi et al., 2018; Tang et al., 2020). In this context, lncH19 knockdown has been reported to inhibit EMT in HCC cells by enhancing miR-675 expression, which is involved in sorafenib sensitivity. In brief, H19 promoted sorafenib resistance (Xu et al., 2020). LncRNA-POIR also has an oncogenic effect and suppresses miR-182-5p expression, inhibiting the EMT process and triggering sorafenib sensitivity (Chen et al., 2021). Additionally, small nucleolar RNA host gene 3 (SNHG3) induces EMT and CD151 expression by functioning as a ceRNA for miR-128. LncRNA-SNHG3 can induce sorafenib resistance and promote invasion *in vitro* (Zhang et al., 2019). In contrast, lncLIMT (LINC01089), which reppresses miR-665 expression and EMT, decreases sorafenib resistance. In addition, LIMT inhibits tumor growth *in vivo* in tumor nude mouse models (Sun et al., 2022). MiR-125b-5p is upregulated in sorafenib-resistant HCC cell lines and its overexpression induces EMT by repressing ataxin 1 (ATXN1) expression. Thus, it was reported that miR-125b-5p enhances sorafenib resistance *in vivo* (Hirao et al., 2021).

Besides Sorafenib, TACE with doxorubicin and cisplatin is used in HCC advanced patients (Lu et al., 2017; Couri and Pillai, 2019).

Doxorubicin (Adriamycin, DOX) is an anthracycline drug used as an antineoplastic agent. The most known mechanism of action involves the interaction with topoisomerase IIα (TOP2A) (Tewey et al., 1984) and the activation of apoptosis (Roos and Kaina, 2013). Anthracycline drug resistance is caused by the incapability of DOX to accumulate in the nucleus (Cox and Weinman, 2016). For instance, Zhang et al. (2021) reported that overexpression of linc-ROR (long intergenic non-protein coding RNA (linc)-regulator of reprogramming) increases DOX resistance in HCC cell lines by TWIST upregulation. Also, circFoxo3 has higher expression in adriamycin-resistant patients. It has been shown that circFoxo3 via miR-199a enhances ABCC1 expression, a known protein involved in drug resistance. Moreover, the downregulation of miR-199a promoted EMT signaling in HCC cells and reversed circFoxo3 inhibition effects (Huang et al., 2020).

Li et al. (2020) identified that circ_0003998 downregulation facilitated DOX-sensitivity by E2F Transcription Factor 3 (E2F3) regulation. They further identified circ_0003998 as a sponge of miR-218-5p and Eukaryotic initiation factor 5A2 (EIF5A2) as a direct target of miR (Li et al., 2020). Moreover, EIF5A2 is involved in genistein resistance, an essential anti-tumoral phytoestrogen that promotes apoptosis (Sarkar and Li, 2002) and inhibits EMT and stemness. MiR-1275 is a tumor suppressor that can bind 3′-UTR EIF5A2 as a protein that upregulated PI3K/Akt and EMT pathways. MiR-1275 was expressed at a higher level by genistein treatment (Yang et al., 2022). Furthermore, it has been shown that miR-140-5p is involved in drug resistance in HCC cells. In brief, miR-140-5p improves DOX sensitivity through PIN1 depletion (Gao et al., 2021) and catalpol sensitivity through EMT suppression (Wu et al., 2021).

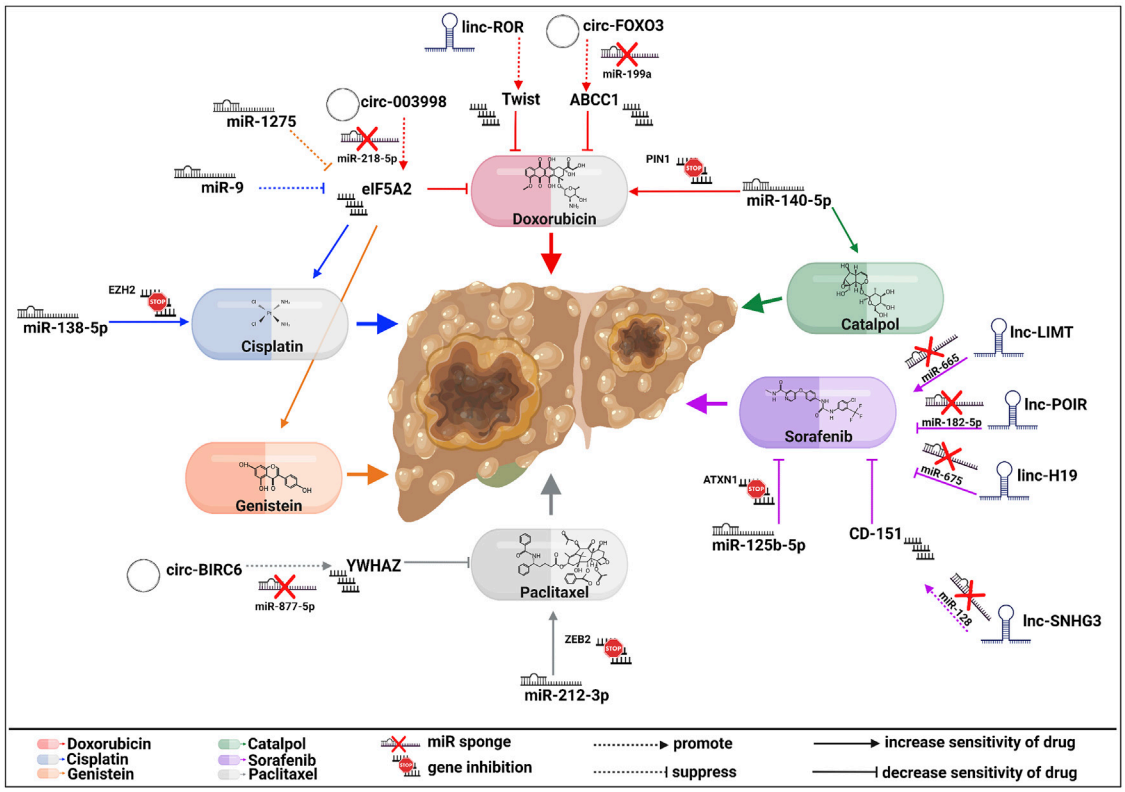

FIGURE 2
Molecular actions of EMT-related ncRNA axes in HCC drug resistance. Multiple regulatory components either increase or decrease sensitivity to sorafenib, paclitaxel, genistein, cisplatin, doxorubicin, or catalpol, affecting HCC progression. The signaling pathways of every drug are represented by different colors, as seen above (created with biorender.com accessed on July 2023).

Cisplatin is a chemotherapeutic that inhibits transcription and replication, inducing apoptosis and necrosis in HCC cells (Ishikawa, 2009). It has been shown that miR-9 increases cisplatin sensitivity *in vitro* and *in vivo* by targeting EIF5A2 and EMT process. Besides that, EIF5A2 depletion decreases vimentin expression and increases E-cadherin in HCC cell lines (Bao et al., 2020). Another ncRNA involved in cisplatin sensitivity is miR-138 by its direct target, enhancer of zeste homolog 2 (EZH2). This miRNA upregulates EMT markers; therefore, the miR-138/EZH2/EMT axis could regulate cisplatin resistance (Zeng et al., 2021), also involved in radiosensitivity. Bai et al. (2022) show that miR-138 is downregulated in HCC tissue and its expression is indirectly correlated with EZH2 expression, which is a direct target of miR-138-5p. By RNA-seq, they observed that miR-138-5p upregulation inhibits HIF-1α and EMT (Bai et al., 2022). Moreover, Lu et al. (2022) reported that miR-138-5p is negatively regulated by circ-TLK1.

Paclitaxel—a microtubule-stabilizing molecule, induces cell death (Weaver, 2014). As mentioned above, paclitaxel (PTX) is another drug whose resistance could be caused by different signaling pathways, including ncRNAs and EMT (Ashrafizadeh et al., 2021). Liu et al. (2020) pointed out circ-BIRC6 (circRNA baculoviral IAP repeat-containing 6) as an inhibitor of PTX sensitivity by sponging miR-8 77-5p to enhance tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta (YWHAZ) expression. Its role in drug resistance has been reported in ovarian cancer (Hong et al., 2018), bladder cancer (Yu et al., 2019), and gastric cancer (Zhao et al., 2021). Furthermore, miR-212-3p is decreased in PTX-resistant cells. This miRNA can bind to 3′UTR ZEB2, thus mediating chemoresistance in HCC cells. Transfection of miR-212-3p in resistant cells inhibited ZEB2 expression, reversing EMT (Yang et al., 2020). Figure 2 summarizes the ncRNAs axes involved in HCC drug resistance.

These investigations show the complex and dual role of ncRNAs in EMT. The exact mechanism by which every ncRNA is involved in the HCC will be difficult to decode because of its functions in many hepatocellular processes. One way to start is by classifying the miRNAs based on their direct or indirect impact on the EMT process. Undoubtedly, future studies are necessary to report new miRNAs associated with HCC-EMT and to map their function in this process, which can lead to the development of novel therapies.

Therefore, to translate ncRNAs in a therapeutic situation, tools must be developed to analyze these ncRNA axes functionally and to devise therapy strategies, so as to overcome off-target and toxicity consequences.

4 EMT-associated exosomal ncRNAs in HCC

Exosomes can be found in all human body fluids (blood, urine, saliva, ascites, cerebrospinal and synovial fluids) (Jiang

et al., 2022). They are extracellular 30–100 nm vesicles (EVs) having a lipid bilayer; they are generated from the luminal membranes of multivesicular bodies (MVBs) and released into the extracellular matrix after MVBs fusion with the cell membrane (Kim et al., 2020). The primary physiological role of exosomes is to mediate cell-cell communication by transferring bioactive molecules, such as proteins or nucleic acids (Chen et al., 2021), thus being one of the most studied tools for the interchange of substances between tumor cells and the tumor microenvironment (Jiang et al., 2022).

In the last decade, more studies have highlighted the regulatory effects of different bioactive molecules delivered by exosomes, such as ncRNAs, in the EMT process in various types of cancers, including HCC. Interestingly, they can promote or suppress the EMT phenomena in HCC cells.

According to RNAseq investigation, exosomal miR-92a-3p expression level increases in two established high-metastatic HCC cell lines (97 hm and Huhm). Besides, treatment with high-metastatic HCC-derived exosomal miR-92a-3p facilitates the aggressiveness of HCC cells via PTEN inhibition and Akt/Snail signaling activation, promoting EMT (Yang et al., 2020). Similarly, high levels of miR-4800-3p were found in Huh7 cell-derived exosomes. Thus, Lin et al. (2022) demonstrated that exosomal miR-4800-3p heightened the progression of HCC by regulating the Hippo signaling pathway and targeting STK25 in both *in vitro* and *in vivo* experiments. Moreover, the treatment of low metastatic HCC cells with exosomal miR-4800-3p downregulates the expression of E-cadherin and ZO-1 and increases the expression of N-cadherin, activating the EMT process (Lin et al., 2022).

Interestingly, M2 macrophages can influence tumor development by secreting various cytokines and exosomes that can be loaded with specific miRNAs. For instance, miR-660-5p-loaded M2 exosomes augmented EMT and enhanced the tumorigenic ability in HCC cells through downregulating Kruppel-like factor 3 (KLF3) expression (Tian et al., 2021).

Human umbilical cord mesenchymal stem cells (hucMSCs) have low immunogenicity and high proliferation and differentiation potential. Additionally, the treatment of HCC cells with hucMSC-Exo upregulates miR-451a. This miRNA inhibits a disintegrin and metalloprotease 10 (ADAM10), thus reducing EMT and aggressive phenotypes of HCC (Xu et al., 2021).

Several studies showed that TGF-β treatment induces EMT (Miyazono, 2009; Lin et al., 2020; Kim et al., 2021) and treatment with exosomes derived from these cells increases proliferation and metastasis in HCC cells (Lin et al., 2020) through intercellular communication. Lin et al. (2020) reported that 119 miRNAs are upregulated, such as miR-125b-5p, 374a-5p, miR-24-3p, miR-200b-3p, and miR-21-5p, and 186 are downregulated in EMT-Hep3B-derived exosomes (EMT-Hep3B exo), as compared to Hep3B exo. Moreover, treatment with EMT-Hep3B exo with miR-374a-5p interference inhibits hepatocellular metastasis by upregulation of growth arrest and DNA damage 45-alpha (GADD45A), a cell growth suppressor (Lin et al., 2020). In contrast, Huh7 cell-derived exosomes loaded with miR-125b (Exo-125b) blocks EMT and suppresses metastatic potential via inhibiting TGF-β1/SMAD pathways (Kim et al., 2021). Similarly, miR-374c-5p was found to be downregulated in the EMT model and transferred by exosomes derived from bone marrow mesenchymal stem cells (BMSC) suppresses EMT via targeting LIM domain kinase 1 (LIMK1) and inhibiting Wnt/β-catenin and TGF-β1 axes in HCC cells (Ding et al., 2023).

Yao et al. (2022) identified that lncRNA THEMIS2-211 is upregulated in plasma-derived exosomes from HCC patients. Knockdown of THEMIS2-211 increases E-cadherin and decreases N-cadherin and vimentin in HCC cells. Mechanistically, they showed that THEMIS2-211 is an oncogene that promotes proliferation, migration, invasion, and EMT by sponging miR-940 and increasing SPOCK1 expression (Yao et al., 2022).

Circ-0004277 and lncRNA PRR34-AS1 transfer via exosomes to human hepatic cells increases the malignant phenotype (Zhu et al., 2020; Zhang et al., 2022). Thus, PRR34-AS1 enhanced Rab27a expression to increase the exosome secretion of VEGF and TGF-β in HCC cells and transmitted them into the human liver epithelial (THLE-3) cells (Zhang et al., 2022).

In summary, these studies prove that exosomes act as ncRNAs cargo for tumor cells and have distinct regulatory effects on the EMT process in HCC and various underlying processes. Although exosomes are promising therapy in cancer, improvement of their purification, and additional studies on the interaction and mechanisms with other types of cells remain the main problems to be solved in their uses.

5 Conclusion and future perspectives

The development of transcriptomics approaches in the last decade has highlighted the essential roles of ncRNAs in cancer (Slack and Chinnaiyan, 2019; Winkle et al., 2021). The formation of ncRNA axes starts to become an essential tool in various cellular mechanisms, and its role in the progression of HCC is decisive (Wong et al., 2018). Furthermore, it will be crucial to comprehend how ncRNA axes regulate migration, proliferation, and EMT in HCC cells, so as to generate cutting-edge therapeutic medications based on ncRNAs, to prevent and manage HCC.

Taking together these observations, we find that defining ncRNA pathways in direct and indirect mechanisms could map a precise road to a therapeutic target as close to a clinical necessity as possible. The EMT-related miRNAs' direct mechanism of action could be a promissive path in developing new therapies against metastasis. However, more research is needed to understand how these miRNA axes work and to determine which transcripts are valuable targets. Undoubtedly, since a single miRNA could have several targets and can affect more therapeutic drugs, its use as a new therapy in cancer requires an in-depth study of the mechanisms involved.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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