Table SI. Exosomal circRNAs and circRNAs involved in HCC treatment resistance.

A, Upregulated					
First author, year	circRNA	Influence	Treatment method	Mechanism	(Refs.)
Dong *et al*, 2024	circUPF2	Drug resistance	Sorafenib	Enhances sorafenib resistance by promoting SLC7A11 expression and inhibiting ferroptosis in HCC cells.	(17)
Zhang *et al*, 2025	circTTC13	Drug resistance	Sorafenib	Promotes sorafenib resistance in HCC through the inhibition of ferroptosis by targeting the miR-513a-5p/SLC7A11 axis.	(123)
Xu *et al*, 2020	circRNA-SORE	Drug resistance	Sorafenib	By binding to YBX1, it reduces its ubiquitination and degradation, affecting the expression of YBX1 downstream gene targets and thus enhancing resistance to sorafenib.	(18)
Xu *et al*, 2020	circRNA-SORE	Drug resistance	Sorafenib	Isolation of miR-103a-2-5p and miR-660-3p by acting as a miRNA sponge, thereby competitively activating the Wnt/β-catenin pathway and inducing	(8)

				sorafenib resistance.	
Feng *et al*, 2025	CSF3R-AS	Drug resistance	Sorafenib	Promotes HCC progression and sorafenib resistance through the CSF3R/JAK2/STAT3 positive feedback loop.	(127)
Ruan *et al*, 2023	cDCBLD2	Drug resistance	Sorafenib	By competitively binding to miR-345-5p, it increases the stability of TOP2A mRNA and reduces the therapeutic effect of sorafenib by inhibiting apoptosis.	(189)
Yang and Wu, 2022	circ-001241	Drug resistance	Sorafenib	Promotes sorafenib resistance in HCC by regulating the miR-21-5p/TIMP3 axis.	(190)
Zhang *et al*, 2022	hsa_circ_0000615	Drug resistance	Sorafenib	-	(182)
Qiu and Zeng, 2022	hsa_circ_0006988	Drug resistance	Sorafenib	Regulation of IGF1 levels by sponging miR-15a-5p promotes sorafenib resistance in HCC cells.	(191)
Hao *et al*, 2022	circPAK1	Drug resistance	Lenvatinib	Competitively binds to YAP 14-3-3ζ, thereby promoting YAP nuclear localization, leading to inactivation of	(77)

				the Hippo signaling pathway. Can be transmitted by exosomes to promote drug resistance.	
Zhang *et al*, 2022	circMED27	Drug resistance	Lenvatinib	Acts as a ceRNA of miR-655-3p to enhance HCC cell resistance to lenvatinib by upregulating USP28 expression.	(133)
Tang *et al*, 2025	circRNA-mTOR	Drug resistance	Lenvatinib	circRNA-mTOR promotes HCC cell stemness and lenvatinib resistance by directly binding to PSIP1, which modulates PSIP1 nuclear translocation to activate the PSIP1/c-Myc signaling pathway.	(134)
Yang *et al*, 2025	circCCNY	Drug resistance	Lenvatinib	Enhances lenvatinib efficacy and prevents immune escape in HCC by promoting HSP60 degradation via SMURF1 to inhibit MAPK signaling and simultaneously blocking the MAPK/c-Myc/PD-L1 axis to increase $CD8^+$ T cell infiltration.	(135)
Cao *et al*,	hsa_circ_0007132	Drug resistance	Lenvatinib	Mediates lenvatinib resistance by	(138)

2025				stabilizing the NONO protein (through inhibition of ubiquitination), which then promotes the nuclear export and subsequent increased expression of the ZEB1 oncogenic factor.	
Yuan *et al*, 2025	circPIK3C3	Drug resistance	Lenvatinib	Inhibits HCC progression and lenvatinib resistance by suppressing the Wnt/β-catenin pathway via the miR-452-5p/SOX15 axis.	(139)
Gong *et al*, 2024	circDCAF8	Drug resistance	Regorafenib	Promotes NAP1L1 expression through sponging miR-217 and confers a drug-resistant phenotype on sensitive HCC cells via exosomes.	(19)
Wang *et al*, 2021	hsa_circ_0032029 and hsa_circ_0008928	drug resistance	Regorafenib	-	(142)
Zhou *et al*, 2022	circZFR	Drug resistance	Cisplatin	Exosome incubation derived from CAFs increased the expression of circZFR in HCC cells and inhibited the STAT3/NF-κB pathway.	(95)
Li *et al*,	circARNT2	Drug resistance	Cisplatin	Regulation of cisplatin resistance	(97)

2021				through the miR-155-5p/PDK1 pathway.	
Li *et al*, 2022	circ_0000098	Drug resistance	DOX	Reduces DOX resistance by decreasing the expression of P-glycoprotein and intracellular ATP levels in HCC cells.	(103)
Wang *et al*, 2025	hsa_circ_0088036	Drug resistance	OXA	Promotes HCC tumorigenesis and OXA resistance by activating the PI3K/Akt and Notch pathways through regulation of the miR-140-3p/KIF2A signaling cascade.	(104)
Li *et al*, 2020	circFBXO11	Drug resistance	OXA	Regulation of OXA resistance in HCC cells via the circFBXO11/miR-605/FOXO3/ABCB1 axis.	(105)
Li *et al*, 2025	circSNX25 (has_circ_0004874)	Drug resistance	Radioresistance	circSNX25-encoded protein promotes radiotherapy resistance in HCC by modulating BAG6 nuclear translocation.	(43)
Yang *et al*, 2019	cZNF292	Treatment resistance	Radioresistance	Increased translocation of SOX9 and subsequent decreased activity of the Wnt/β-catenin pathway is responsible	(111)

				for radiation resistance.	
Zhu *et al*, 2022	circ-LARP1B	Treatment resistance	Radioresistance	Knockdown of circ-LARP1B inhibits HCC tumorigenesis and enhances radiosensitivity by regulating the miR-578/IGF1R axis.	(112)
Chang *et al*, 2023	circRNA-SMARCA5	Treatment resistance	Radioresistance	-	(113)
Yang *et al*, 2024	circROBO1	Treatment resistance	Radioresistance	RAD21 is regulated by targeting miR-136-5p, thereby promoting radiation resistance in HCC.	(115)
Lan *et al*, 2025	circPETH	Drug resistance	Anti-PD1 resistance	circPETH-147aa maintains HuR S100 phosphorylation via the MEG pocket, enhancing HuR-dependent SLC43A2 mRNA stability to promote HCC amino acid uptake, thereby metabolically crippling $CD8^+$ T cells and driving immune resistance.	(41)
Fu *et al*, 2025	circ-CDYL	Drug resistance	Anti-PD1 resistance	Confers HCC immunotherapy resistance by binding to and stabilizing HRNR, which activates the mTORC1 pathway to increase PD-L1 expression	(148)

				and PD-L1-exosome secretion, suppressing $CD8^+$ T cell function.	
Hu *et al*, 2023	circCCAR1	Drug resistance	Anti-PD1 resistance	$CD8^+$ T cell dysfunction caused by the PD-1 protein on stable $CD8^+$ T cells promotes resistance to PD-1 immunotherapy.	(149)
Lu *et al*, 2021	circTMEM181	Drug resistance	Anti-PD1 resistance	Sponges miR-488-3p to increase the expression of CD39 on macrophages and interacts with CD37 on HCC cells to continuously activate the ATP-adenosine pathway, impair the function of $CD8^+$ T cells and create a tumor microenvironment that is resistant to anti-PD-1.	(150)
Zhang *et al*, 2020	circUHRF1	Drug resistance	Anti-PD1 resistance	Inhibits NK cell function by degrading miR-449c-5p to upregulate TIM-3 expression.	(151)
Huang *et al*, 2020	circMET	Drug resistance	Anti-PD1 resistance	Induces HCC immune tolerance and resistance to anti-PD-1 therapy via the Snail/DPP4/CXCL10 axis.	(152)
Cai *et al*,	circRHBDD1	Drug resistance	Anti-PD1 resistance	Influences resistance to anti-PD-1	(153)

2022				therapy via the circRHBDD1/YTHDF1/PIK3R1 axis.	
Ye *et al*, 2023	circSOD2	Drug resistance	Anti-PD1 resistance	Promotes immune evasion and anti-PD-1 resistance through the miR-497-5p/ANXA11 axis.	(154)
Huang *et al*, 2022	circGSE1	Treatment resistance	Immunotherapy resistance	Inducing Tregs expansion via regulating the miR-324-5p/TGFBR1/Smad3 axis causes HCC immune evasion.	(160)
Wang *et al*, 2021	hsa_circ_0074854	Treatment resistance	Immunotherapy resistance	Exosomes containing downregulated hsa_circ_0074854 inhibit macrophage M2 polarization, thereby suppressing the migration and invasion of HCC in both *in vitro* and *in vivo* settings.	(68)
B, Downregulated					
First author, year	circRNA	Influence	Treatment method	Mechanism	(Refs.)
Dong *et al*, 2021	circMEMO1	Sensitivity	Sorafenib	It exerts its effect through the miR-106b-5p/TET1/5hmC/TCF21 axis and the EMT process. As a key epigenetic	(129)

				modifier, it can regulate the sensitivity of HCC to sorafenib treatment.	
Song *et al*, 2023	circZKSCAN1	Sensitivity	Sorafenib	By encoding circZKSaa, the PI3K/AKT/mTOR pathway is inhibited by promoting mTOR ubiquitination, making HCC sensitive to sorafenib.	(42)
Li *et al*, 2023	circITCH	Sensitivity	Sorafenib	Enhances the sensitivity of sorafenib-resistant HCC cells to sorafenib by regulating the miR-20b-5p/PTEN/PI3K/Akt signaling cascade.	(192)
Zhang *et al*, 2024	circDDX17	Sensitivity	Sorafenib	Inhibits PTEN expression and activates the PI3K/AKT pathway by competitively binding miR-21-5p; its upregulation enhances sensitivity to sorafenib, promotes apoptosis and inhibits the EMT process.	(193)
Wang *et al*, 2022	hsa_circRNA_102049	Sensitivity	Sorafenib	Upregulates the expression of the RELN gene via sponging hsa-miR-214-3p.	(194)
Yang *et*	circCCNY	Sensitivity	Lenvatinib	Enhances lenvatinib sensitivity and	(135)

al, 2025				suppresses immune evasion in HCC by serving as a scaffold for SMURF1-mediated HSP60 degradation.	
Qin *et al*, 2021	circ-G004213	Sensitivity	Cisplatin	Promotes cisplatin sensitivity by regulating miR-513b-5p/PRPF39, and circ-G004213 is positively correlated with the prognosis of patients with HCC after TACE.	(94)
Luo *et al*, 2019	circRNA_101505	Sensitivity	Cisplatin	Promotes NOR1 expression via sponging miR-103 to make HCC cells sensitive to cisplatin.	(66)
Chen *et al*, 2019	circ_0003418	Sensitivity	Cisplatin	Promotes the sensitivity of HCC cells to cisplatin by activating the Wnt/β-catenin signaling pathway in HCC cells.	(98)
Yuan *et al*, 2025	circTMEM56	Sensitivity	Radiosensitivity	Enhances radiotherapy efficacy in HCC via dendritic cell-mediated cGAS-STING activation.	(107)
Lin *et al*, 2024	circNOP14	Sensitivity	Radiosensitivity	Increases DNA damage induced by irradiation by interacting with Ku70 and preventing its nuclear	(109)

				translocation.	
Wang *et al*, 2023	circ_0071662	Sensitivity	Radiosensitivity	-	(114)
Shi *et al*, 2021	hsa_circ_0007456	Sensitivity	NK cell	Modulates drug resistance via sponging miR-6852-3p and regulates the expression of ICAM-1 in HCC cells.	(166)

ABCB1, ATP Binding Cassette Subfamily B Member 1; ANXA11, Annexin A11; BAG6, BCL2 associated athanogene 6; CAFs, cancer-associated fibroblasts; cGAS, cyclic GMP-AMP synthase; ceRNA, competing endogenous RNA; c-Myc, cellular myelocytomatosis oncogene; CSF3R, colony stimulating factor 3 receptor; CXCL10, C-X-C motif chemokine ligand 10; DPP4, dipeptidyl peptidase 4; DOX, doxorubicin; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; HRNR, hornerin; HuR, Hu antigen R; ICAM-1, intercellular adhesion molecule 1; IGF1, insulin like growth factor 1; IGF1R, IGF1 receptor; JAK2, Janus kinase 2; KIF2A, kinesin family member 2A; Ku70, X-ray repair cross-complementing protein 6; miRNA, microRNA; NAP1L1, nucleosome assembly protein 1 like 1; NF-κB, nuclear factor κB; NK cell, natural killer cell; NONO, non-POU domain containing octamer binding; NOR1, oxidored-nitro domain-containing protein 1; OXA, oxaliplatin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDK1, pyruvate dehydrogenase kinase 1; PSIP1, PC4 and SFRS1 interacting protein 1; RAD21, RAD21 cohesin complex component; RELN, reelin; SMURF1, SMAD specific E3 ubiquitin protein ligase 1; SOX, SRY-box transcription factor; STING, stimulator of interferon genes; TACE, transarterial chemoembolization; TCF21, transcription factor 21; TGFBR1, transforming growth factor β receptor 1; TET1, ten-eleven translocation methylcytosine dioxygenase 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TIMP3, TIMP metallopeptidase inhibitor 3; TOP2A, DNA topoisomerase II α; Tregs, regulatory T cells; USP28, ubiquitin specific peptidase 28; YAP, Yes associated protein; YBX1, Y-box binding protein 1; YTHDF1, YTH N6-methyladenosine RNA binding protein 1; ZEB1, zinc finger E-Box binding homeobox 1; 5hmC, 5-hydroxymethylcytosine.