Supplementary Table 1 HBV-dysregulated miRNAs that play different roles in HBV-HCC

Process	HBV-dysregulated miRNAs
Cell cycle	A: miR-106b[1], miR-331-3p[2],miR-3188[3]. B: miR-18a[4], miR-30e-5p[5], miR-136-5p[6], and miR-0308-3p[6], miR-338-3p[7]. C: let-7[8], miR-15a/16[9], miR-145[10], miR-148a[11], miR-200a-3p[12], miR-203a[13], miR-221[14], miR-222[15].
Proliferation	A: miR-19a[16], miR-30b-5p[17], miR-106b[1], miR-135a-5p[18], miR-135b[19], miR-142-3p[20], miR-155[21, 22], miR-181a [23-25], miR-181b[26], miR-211-5p[27], miR-215[28], miR-222-3p[29], miR-224[30], miR-331-3p[2, 31, 32], miR-362[16], miR-382[16], miR-499a[33], miR-1269b[34], miR-3188[3], miR-5188[35]. B: let-7[36], let-7a[37], miR-7 [38, 39], miR-15a/miR-16[9, 40, 41], miR-18a[4], miR-18b[42], miR-30e[43], miR-34a[44, 45], miR-98-5p[46], miR-100[47], miR-101-3p[48], miR-122[49, 50], miR-125a-5p[51], miR-136-5p[6], miR-148a[52], miR-200a-3p[53], miR-216b[54], miR-0308-3p[55], miR-325-3p[56], miR-329[57], miR-338-3p[7, 58], miR-340-5p[59], miR-424-5p[60], miR-520b[61], miR-520e[62], miR-1236[57]. C: miR-15b[63], miR-21[64-66], miR-22[67, 68], miR-23a[69], miR-29c[70], miR-34c[71], miR-101-3p[72], miR-124[73], miR-129-2[74, 75], miR-129-5p[76], miR-132[77], miR-137[78], miR-145[10, 15], miR-146a-5p[79], miR-152[80], miR-154[81], miR-181a[82], miR-192[83], miR-200a-3p[12], miR-200a/200b[84], miR-203a[13, 85], miR-205[86], miR-221[14], miR-221-3p[87], miR-223[88], miR-371a-5p[89], miR-375[87, 90], miR-384[91], miR-429[84, 92], miR-539[93], miR-545/374a[94],miR-548p[95], miR-602[96], miR-627-3p[97], miR-933[98], miR-1305[99].
Apoptosis	A: miR-135a-5p[18], miR-146a-5p[79], miR-155[22], miR-181a[25, 82], miR-192-5p[100], miR-194-5p[100], miR-211-5p[27], miR-331-3p[32], miR-3188[3]. B: miR-15a/16[9], miR-30e-5p[5], miR-98-5p[46], miR-101-3p[48], miR-125a-5p[51], miR-136-5p[6], miR-200a-3p[53], miR-216b[54], miR-325-3p[56], miR-340-5p[59], miR-424-5p[60], miR-520e[62]. C: miR-21[65, 66], miR-29c[70], miR-34c[71], miR-101-3p[72], miR-145[10], miR-152[80], miR-192/215-5p[100], miR-203a[13],

	miR-222-3p[29], miR-548p[95], miR-602[96].
Migration and invasion	A: miR-19a[24], miR-29a[101], miR-135b[19], miR-142-3p[20], miR-143[102], miR-155[22], miR-181a[24],miR-211-5p[27], miR-305-5p[17], miR-362[24], miR-382[24], miR-382-5p[103], miR-520c-3p[104], miR-1269b[34], miR-3188[3], miR-5188[35].a B: miR-34a[44], miR-98-5p[46], miR-101-3p[48], miR-122[49, 50], miR-136-5p[6], miR-148a[52], miR-200a-3p[53], miR-216b[54], miR-338-3p[58], miR-424-5p[60] miR-340-5p[105], miR-924[106]. C: miR-7[107], miR-21[107, 108], miR-22[109], miR-101-3p[72], miR-103[107] miR-107[107], miR-140-5p[110], miR-152[80], miR-192[83], miR-200a-3p[12], miR-203a[85], miR-221-3p[87], miR-224[30], miR-371a-5p[89], miR-375[87], miR-384[91], miR-499a[33], miR-545/374a[94], miR-627-3p[97].
Epithelial–mesenchymal transition (EMT)	A: miR-371a-5p[89], miR-6755-5p[111] B: miR-122[112], miR-140-5p[110] C: miR-34a[44], miR-148a[52], miR-340-5p[105], miR-520c-3p[104], miR-924[106], miR-5188[35]
HBV replication	A: miR-125a-5p[113, 114], miR-146a-5p[115], miR-203[116], miR-539[93], miR-548ah [117], miR-802[118]. B: miR-98-5p[46], miR-125a-5p[51], miR-138-5p[119], miR-154[81], miR-192-3p[120, 121], miR-200a-3p[53], miR-204[122, 123], miR-424-5p[60], miR-1236[122]. C: miR-29c[70], miR-34c[71], miR-122[124], miR-210-3p[125], miR-221-3p[87], miR-325-3p[56], miR-375[87], miR-933[98].

A: HBV-upregulated miRNAs; B: HBV-downregulated miRNAs; C: HBV-dysregulated miRNAs whose underlying mechanism of dysregulation remains further investigation, or which are inferred from their target genes.

Supplementary Table 2 Functions of HBV-dysregulated miRNAs in promoting HCC

miRNA	HBV protein	Expression	Target genes	Abnormal function in HBV-HCC	Note	Ref
let-7	HBx	down	STAT3	suppressing cell proliferation		[36]
let-7a	HBV mRNA	down	c-myc, K-RAS, and CCR7	suppressing cell proliferation		[37]
let-7a	HBV	up	——	promoting HBV replication		[126]
let-7g	HBV mRNA	down	——	inhibiting HBV replication		[127]
miR-7	HBx	up	EGFR/Raf/EKERK/PI3K-Akt	suppressing cell proliferation		[38]
miR-7	HBV, HBx	up	mapsin	promoting cell migration and invasion, conferring HBx-mediated anoikis resistance and doxorubicin resistance	*	[107]
miR-15a	HBV mRNA	down	Smad7/TGF-β	inhibiting tumor growth, suppressing cell proliferation, sensitizing TGF-β1-induced apoptosis	*	[41]
miR-15a/16-1	HBV	down	ANLN	inhibiting tumor growth, increasing poly-nucleated morphology HCC cells and inducing DNA damage	*	[40]
miR-15a/16	HBx	down	——	suppressing cell proliferation, decelerating cell cycle		[9]

				progression, inducing apoptosis		
miR-15a/16	HBV mRNA	down	−−	inducing etoposide-induced apoptosis		[128]
miR-15b	HBx	down	FUT2/Globo H	inhibiting tumor growth, suppressing cell proliferation		[63]
miR-18a	HBx	down	CTGF	suppressing cell proliferation, decelerating cell cycle progression		[4]
miR-18b	HBx	down	NUSAP1	inhibiting tumor growth, suppressing cell proliferation		[42]
miR-19a	HBV	up	PTEN/Akt	enhancing cell proliferation, promoting cell migration and invasion		[24]
miR-19a	HBV, HBx	up	PTEN	enhancing cell proliferation		[88]
miR-21	HBV, HBx	down	PTEN	enhancing cell proliferation	*	[15]
miR-21	HBx	up	IL-12	enhancing cell proliferation, inhibiting cell apoptosis		[65]
miR-21	HBx	up	PTEN/PI3K/Akt/MMP2	promoting cell migration and invasion		[108]
miR-21	HBx	up	−−	promoting tumor growth, enhancing cell proliferation		[64]

miR-21	HBx	up	PDCD4	promoting tumor growth, enhancing cell proliferation, inhibiting cell apoptosis	*	[66]
miR-21	HBV, HBx	up	mapsin	promoting cell migration and invasion, conferring HBx-mediated anoikis resistance and doxorubicin resistance	*	[107]
miR-22	HBV	down	CDKN1A	suppressing cell proliferation, inhibiting the secretion of HBV		[67]
miR-22	HBV	down	——	inhibiting cell migration and invasion		[109]
miR-22-3p	HBV	down	NRAS/Raf/MEK/ERK	suppressing cell proliferation	*	[68]
miR-23a	HBV	down	CCL22	inhibiting tumor growth, inhibiting Tregs recruitment		[69]
miR-29a	HBx	up	PTEN	promoting cell migration		[101]
miR-29c	HBV	down	TNFAIP3	suppressing cell proliferation, inducing cell apoptosis, inhibiting HBV replication, inhibiting the secretion of HBV		[70]
miR-30b-5p	HBp	up	MINPP1	promoting tumor growth, enhancing cell proliferation, promoting cell migration and		[17]

				invasion, regulating glycolytic bypass metabolism		
miR-30e	HBx	down	P4H2	inhibiting tumor growth, suppressing cell proliferation		[43]
miR-30e-5p	HBV	down	MAP4K4/NFAT5/DARS2	Decelerating cell cycle progression and inducing apoptosis	*	[5]
miR-34a	HBV	down	CCL22	inhibiting tumor growth and metastases, inhibiting Tregs recruitment		[45]
miR-34a	HBx	down	IKKβ/NF-κB/HMGB1	inhibiting tumor growth and metastases, inhibiting EMT progress and angiogenesis		[44]
miR-34c	HBV	down	TGIF2	inhibiting tumor growth, suppressing cell proliferation, inducing cell apoptosis, inhibiting HBV replication, inhibiting the secretion of HBV		[71]
miR-93	HBV	down	MICA	——		[129]
miR-98-5p	HBV	down	NIK	inhibiting tumor growth, suppressing cell proliferation, inducing cell apoptosis,		[46]

				inhibiting cell migration and invasion, inhibiting the secretion of HBV		
miR-100	HBV polymerase	binding inhibition	PLK1	inhibiting tumor growth, suppressing cell proliferation		[47]
miR-101	HBV, HBx	down	DNMT3A/RASSF1/PRDM2/GSTP1	affecting DNA methylation of several tumor-suppressor gene promoter regions		[130]
miR-101-3p	HBV	down	Rab5a	suppressing cell proliferation, inducing cell apoptosis, inhibiting cell migration		[48]
miR-101-3p	HBV	down	Rap1b	suppressing cell proliferation, inducing cell apoptosis, inhibiting cell migration		[72]
miR-103	HBV, HBx	up	mapsin	promoting cell migration and invasion, conferring HBx-mediated anoikis resistance and doxorubicin resistance	*	[107]
miR-106b	HBe	up	retinoblastoma	enhancing cell proliferation, accelerating cell cycle progression		[1]

miR-107	HBV, HBx	up	mapsin	promoting cell migration and invasion, conferring HBx-mediated anoikis resistance and doxorubicin resistance	*	[107]
miR-122	HBx-LINE1	down	β-catenin/E-cadherin	suppressing cell proliferation, inhibiting cell migration and invasion, EMT		[112]
miR-122	HBV mRNA	down	PBF/PTTG1	inhibiting tumor growth, suppressing cell proliferation, inhibiting cell migration and invasion		[49]
miR-122	HBV, HBx	down	CCNG1/P53	suppressing cell proliferation, decelerating cell cycle progression	*	[131]
miR-122	HBV	down	G9a	suppressing cell proliferation, inhibiting cell migration and invasion		[50]
miR-122	HBV, HBx	down	Cyclin G1	suppressing cell proliferation		[88]
miR-122	HBV	down	NDRG3	suppressing cell proliferation, inhibiting HBV replication, inhibiting the secretion of HBV		[124]

miR-124	HBx	down	PI3K/Akt	inhibiting tumor growth, suppressing cell proliferation, suppressing CSC differentiation	[73]
miR-125a	HBx	up	−−	interfering with the HBV translation	[113, 114]
miR-125a-5p	HBV	down	ErbB3	suppressing cell proliferation, inducing cell apoptosis, inhibiting the secretion of HBV	[51]
miR-129-2	HBV	down	SOX4/β-catenin/TCF	suppressing cell proliferation	[74, 75]
miR-129–5p	HBx mRNA	down	ZBTB20/EGFR	suppressing cell proliferation	[76]
miR-132	HBx	down	Akt	suppressing cell proliferation	[77]
miR-135a-5p	HBc	up	VAMP2	enhancing cell proliferation, inhibiting cell apoptosis, preventing Doxorubicin hydrochloride-induced apoptosis	[18]
miR-135b	HBx	up	APC/Wnt/β-catenin	promoting tumor growth, enhancing cell proliferation, promoting cell migration and invasion	[19]

miR-136-5p	HBV	down	NACC1	suppressing cell proliferation, decelerating cell cycle progression, inducing cell apoptosis, inhibiting cell migration and invasion	[6]
miR-137	HBx	down	Notch1	suppressing cell proliferation	[78]
miR-138	HBV	down	PD-1	regulating cytokine secretion of T cells and improving T-cell immune responses	[132]
miR-138-5p	HBV	down	TNFAIP3	inhibiting HBV replication, inhibiting the secretion of HBV	[119]
miR-140-5p	HBV	down	Slug	inhibiting cell migration and invasion and EMT	[110]
miR-142-3p	HBV	up	SLC3A2	enhancing cell proliferation, promoting cell migration and invasion, affecting the ferroptosis lipid metabolism of M1 macrophages.	[20]
miR-143	HBx	up	FNDC3B	promoting cell migration and invasion	[102]
miR-145	HBV, HBx	down	MAP3K	suppressing cell proliferation *	[15]

miR-145	HBx	down	CUL5	suppressing cell proliferation, decelerating cell cycle progression, inducing apoptosis	[10]
miR-146a	HBV	up	STAT1	suppressing IFN-induced anti-HBV effect	[133]
miR-146a-5p	HBx, HBc	up	XIAP/MDM2/p53	promoting HBV replication	[115]
miR-146a-5p	HBV, HBx, HBc	up	——	enhancing cell proliferation, inhibiting cell apoptosis, promoting HBV replication	[79]
miR-148a	HBx	down	HPIP/AKT/ERK/FOXO4/ATF5/mTOR	inhibiting tumor growth, suppressing cell proliferation, inhibiting cell migration and invasion, EMT	[52]
miR-148a	HBx	up	PTEN/PI3K/Akt/β-catenin	enhancing cell proliferation, accelerating cell cycle progression, promoting cell migration	[11]
miR-148a/148b	HBV	down	HLA-G	enhanced NK cytolysis against hepatoma cells	[134]
miR-152	HBx	down	DNMT1/RIZ1/	——	[135]

miR-152	HBV	down	HLA-G	enhanced NK cytolysis against hepatoma cells	[134]
miR-152	HBx	down	DNMT1/GSTP/CDH1	leading to global DNA methylation	[136]
miR-152	HBV	down	TNFRSF6B	suppressing cell proliferation, inducing cell apoptosis, inhibiting cell migration	[80]
miR-154	HBV	down	PCNA	suppressing cell proliferation *	[81]
miR-155	HBx	up	ZHX2	enhancing cell proliferation	[21]
miR-155	HBx	up	PTEN	enhancing cell proliferation, inhibiting cell apoptosis, promoting cell migration and invasion	[22]
miR-181a	HBV	up	PTEN/Akt	enhancing cell proliferation, promoting cell migration and invasion	[24]
miR-181a	HBV, HBx	up	PTEN	enhancing cell proliferation, inhibiting cell apoptosis,	[25]
miR-181a	HBV	up	E2F5	promoting tumor growth, enhancing cell proliferation	[23]

miR-181a	HBV	up	Fas	promoting tumor growth, enhancing cell proliferation and inhibiting apoptosis	[82]
miR-181b	HBx	up	ING5	enhancing cell proliferation	[26]
miR-192	HBV	down	TRIM25	suppressing cell proliferation, inhibiting cell migration and invasion,	[83]
miR-192/215-5p	HBx	up	BIM	inhibiting cell apoptosis	[100]
miR-192-3p	HBV	down	XIAP/NF-κB	inhibiting HBV replication	[120]
miR-192-3p			ZNF143/Akt/mTOR	promoting HBV replication	[121]
miR-193b	HBV	down	Mcl-1	sensitizing sorafenib-induced apoptosis	[137]
miR-194-5p	HBx	up	cFLIP	inducing apoptosis	[100]
miR-200a/200b/429	HBx	down	RICTOR	inhibiting tumor growth, suppressing cell proliferation, impairing HCC stem cell properties, sensitizing the response to anti-PD-L1 immunotherapy	* [84, 138]
miR-200a-3p	HBV	down	MAP3K2	suppressing cell proliferation, inducing cell apoptosis, inhibiting cell migration and	[53]

				invasion, inhibiting HBV replication, inhibiting the secretion of HBV	
miR-200a-3p	HBx	down	— —	suppressing cell proliferation, decelerating cell cycle progression, inhibiting cell migration and invasion	[12]
miR-203a	HBx	up	BANF1	increasing HBV titer	[116]
miR-203a	HBs	down	BMI1	inhibiting tumor growth, suppressing cell proliferation, inhibiting cell invasion, sensitizing 5-FU-induced apoptosis, impairing HCC stem cell properties	[85]
miR-203a	HBx	up	Rap1a/MAPK	enhancing cell proliferation, accelerating cell cycle progression, inducing cell apoptosis	[13]
miR-204	HBV	down	— —	inhibiting HBV replication	[122]
miR-205	HBx	down	— —	inhibiting tumor growth, suppressing cell proliferation	[86]

miR-210-3p	HBV	up	IGF2BP2	promoting HBV replication, promoting the secretion of HBV		[125]
miR-211-5p	HBV	up	NR1I3	enhancing cell proliferation, inhibiting cell apoptosis, promoting cell migration and invasion		[27]
miR-215	HBxΔ127	up	PTPRT	promoting tumor growth, enhancing cell proliferation		[28]
miR-216b	HBx	down	IGF2BP2/IGF2/AKT/mTOR/MAPK/ERK	inhibiting tumor growth, suppressing cell proliferation and cell migration, inducing apoptosis		[54]
miR-221	HBx	up	ERα	enhancing cell proliferation, accelerating cell cycle progression		[14]
miR-221-3p	HBV	up	——	enhancing cell proliferation, promoting cell migration and invasion, promoting HBV replication		[87]
miR-222	HBV, HBx	down	p27	Decelerating cell cycle progression	*	[15]

miR-222-3p	HBV	up	THBS1	enhancing cell proliferation, inhibiting cell apoptosis,	[29]
miR-223	HBV, HBx	down	c-myc	suppressing cell proliferation	[88]
miR-224	HBx	up	Sad4	enhancing cell proliferation, promoting cell migration	[30]
miR-0308-3p	HBV	down	CDK6/Cyclin D1	suppressing cell proliferation, decelerating cell cycle progression	[55]
miR-325-3p	HBV	down	AQP5	suppressing cell proliferation, inducing cell apoptosis, inhibiting HBV replication, inhibiting the secretion of HBV	[56]
miR-325-3p	——	——	DPAGT1	sensitizing the response to Doxorubicin chemotherapy	[16]
miR-329	HBV, HBx	down	AFP	suppressing cell proliferation, sensitizing chemotherapy induced apoptosis	* [57]
miR-331-3p	HBV, HBx, HBs	up	ING5	promoting tumor growth, enhancing cell proliferation and inhibiting apoptosis	[32]
miR-331-3p	HBV	up	VHL	enhancing cell proliferation, accelerating cell cycle	* [2, 31]

				progression, inhibiting cell apoptosis		
miR-338-3p	preS2	down	TAZ	inhibiting tumor growth, suppressing cell proliferation, inhibiting cell migration and invasion	*	[58]
miR-338-3p	HBx	down	Cyclin D1	suppressing cell proliferation, decelerating cell cycle progression		[7]
miR-340-5p	HBV	down	STAT3	inhibiting cell migration and EMT		[105]
miR-340-5p	HBV	down	ATF7	suppressing cell proliferation, inducing cell apoptosis		[59]
miR-362	HBV	up	PTEN/Akt	enhancing cell proliferation, promoting cell migration and invasion		[24]
miR-371a-5p	HBV	up	SRCIN1/NF-KB/PTN/Slug	promoting tumor growth, enhancing cell proliferation, promoting cell migration and invasion, promoting angiogenesis and EMT		[89]
miR-373	HBx	down	E-cadherin	——		[139]

miR-375	HBV	down	— —	suppressing cell proliferation, inhibiting cell migration and invasion, inhibiting HBV replication	[87]
miR-382	HBV	up	PTEN/Akt	enhancing cell proliferation, promoting cell migration and invasion	[24]
miR-382-5p	HBc	up	DLC-1	promoting cell migration and invasion	[103]
miR-384	HBV, HBx	down	PTN/PI3K/AKT/mTORC1	inhibiting tumor growth, suppressing cell proliferation, inhibiting cell migration and invasion, suppressing angiogenesis, inhibiting high glucose-induced lipogenesis	[91]
miR-424-5p	HBV	down	TGIF2	suppressing cell proliferation, inducing cell apoptosis, inhibiting cell migration and invasion, inhibiting HBV replication, inhibiting the secretion of HBV	[60]

miR-429	HBx	down	Rab18	suppressing cell proliferation, inhibiting dysregulation of lipogenesis	* [92]
miR-499a	HBV	up	MAPK6	promoting tumor growth, enhancing cell proliferation, promoting cell migration	[33]
miR-520b	HBx	down	HBXIP	enhancing cell proliferation	[61]
miR-520c-3p	HBV, HBx	up	PTEN/AKT/NF-κB	promoting cell migration and invasion and EMT	[104]
miR-520e	HBx	down	EphA2	suppressing cell proliferation, inducing cell apoptosis, inhibiting HBV replication, inhibiting the secretion of HBV	[62]
miR-539	HBx	up	APOBEC3B	enhancing cell proliferation, promoting HBV replication	[93]
miR-545/374a	HBV, HBx	up	ESRRG	enhancing cell proliferation, promoting cell migration	[94]
miR-548ah	HBc	up	HDAC4	promoting HBV replication, promoting the secretion of HBV	[117]
miR-548p	HBx	down	HBXIP	enhancing cell proliferation, inhibiting cell apoptosis,	[95]

miR-602	HBV, HBx	up	RASSF1A	enhancing cell proliferation, inhibiting cell apoptosis,	[96]
miR-620	HBV, HBx	down	AFP	——	[140]
miR-627-3p	HBx	down	HMGA2	suppressing cell proliferation, inhibiting cell migration and invasion,	[97]
miR-802	HBV	up	SMARCE1	promoting HBV replication, promoting the secretion of HBV	[118]
miR-924	HBV	down	CKMT1A	inhibiting cell migration and invasion and EMT	[106]
miR-933	HBV	up	HDAC11	enhancing cell proliferation, promoting HBV replication	[98]
miR-1236	HBV, HBx	down	AFP	suppressing cell proliferation, * sensitizing chemotherapy induced apoptosis	[57]
miR-1236	HBV	down	——	inhibiting HBV replication	[122]
miR-1236	HBV, HBx	down	AFP	——	[140]
miR-1269b	HBx	up	CDC40	enhancing cell proliferation, promoting cell migration and invasion	[34]
miR-1270	HBV, HBx	down	AFP	——	[140]

miR-1305	HBV	down	— —	inhibiting tumor growth, suppressing cell proliferation	[99]
miR-3188	HBx	up	ZHX2/NFYA/NOTCH1	promoting tumor growth, enhancing cell proliferation, accelerating cell cycle progression, inhibiting apoptosis, promoting cell migration and invasion	[3]
miR-3682-3p	HBx	up	FOXO3/PI3K/AKT1/β-catenin/c-Myc	promoting HCC stemness	[141]
miR-5188	HBx	up	FOXO1/β-catenin	enhancing cell proliferation, promoting cell migration and invasion, resisting the effects of chemotherapy 5-FU, CDDP and EPI, promoting HCC stemness	[35]
miR-6755-5p	HBV	up	NDRG2	promoting EMT	[111]

*The functions of miRNAs were inferred from their targets and were not validated.

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