

**Table SI. Roles of sEVs in the initiation and development of HCC.**

Type	Molecule	Function	Signaling/target	Isolation method	Year of publication	(Refs.) <sup>a</sup>
miRNAs	miR-150-3p↓	Inhibits migration and invasion	PTEN	Total Exosome Isolation (Thermo Fisher Scientific, Inc.)	2021	(31)
	miR-92b↑	Impairs the functions of NK cell and promotes migration	CD69	ExoQuick Exosome Precipitation Solution (System Biosciences, Inc.)	2019	(32)
	miR-200b-3p↓	Promotes angiogenesis	ERG	Total Exosome Isolation (Thermo Fisher Scientific, Inc.)	2020	(33)
	miR-32-5p↑	Induces multidrug resistance, angiogenesis and EMT	PI3K/Akt	Ultracentrifugation	2018	(34)
	miR-9-3p↓	Promotes proliferation	ERK/ HBGF-5	Ultracentrifugation	2018	(35)
	miR-93↑	Promotes proliferation and invasion	TIMP2/TP53INP1/CDKN1A	Total exosome isolation kit (Thermo Fisher Scientific, Inc.)	2018	(36)
	miR-1290↑	Promotes angiogenesis	SMEK1	Exosome isolation reagent (Guangzhou RiboBio Co., Ltd.)	2021	(37)
	miR-25-3p↑	Promotes proliferation and migration	TCF21 and HHIP	GST <sup>TM</sup> Exosome Isolation Reagent (Genesee Biotech, Co., Ltd.)	2020	(38)
	miR-296↑	Promotes lymphangiogenesis	EAG1/VEGFA	Ultracentrifugation	2019	(39)
	miR-490↑	Promotes migration	ERK1/2	Total exosome isolation reagent (Carlsbad, CA, US)	2017	(40)
	miR-378b↑	Promotes proliferation and angiogenesis	TGFBR3	ExoQuick Exosome Precipitation Solution (System Biosciences, Inc.)	2021	(41)

	miR-103↑	Promotes migration	VE-Cad/p 120/ZO-1	Unknown	2018	(42)
	miR-320a↓	Promotes proliferation and migration	PBX3-ERK1/2-CDK2	Unknown	2017	(43)
	miR-326↑	Inhibits proliferation, migration and invasion; promotes apoptosis	NF-κB	Exosomes separation kit (ExoEasy Maxi kit, Qiagen GmbH)	2020	(44)
	hsa-miR-24-3p↑	Promotes EMT and migration	TGFβ1	Total Exosome Isolation Reagent (Thermo Fisher Scientific, Inc.)	2020	(45)
lncRNA	PCED1B-AS1↑	Promotes immunosuppression	PD-Ls	Unknown	2021	(46)
	DLX6-AS1↑	Promotes lung migration	miR-15a-5p/CXCL17 axis	Exoquick-TC™ kit (EXOTC50A-1, System Biosciences, Inc.)	2021	(47)
	LINC00161↑	Promotes angiogenesis and metastasis	miR-590-3p/ROCK	Total Exosome Isolation Kit (Invitrogen; Thermo Fisher Scientific, Inc.)	2021	(48)
	SENP3-EIF4A1↑	Promotes apoptosis, and inhibits invasion and migration	ZFP36	ExoQuick™ (System Biosciences, Inc.)	2020	(49)
	lncRNA ROR↑	Inhibits apoptosis and promotes proliferation	Caspase-3/9	Total Exosome Isolation Reagent (Thermo Fisher Scientific, Inc., #4478359)	2019	(50)
	lncRNA FAL1↑	Promote proliferation and migration	miR-1236	ExoQuick TC™ (EXOQ20A-1, System Biosciences, Inc.)	2018	(51)
circRNA	circRNA UHRF1↑	Induces immunosuppression and resistance to anti-PD1 therapy	TIM-3	ExoQuick Exosome Precipitation Solution (SBI System Biosciences, Inc.; cat. no. EXOQ5A-1)	2020	(52)
	circRNA Cdr1as↑	Promotes proliferation and migration	miR-1270	ExoQuick exosome precipitation	2019	(53)

				solution (System Biosciences, Inc.)		
	circRNA SORE↑	Resistance to sorafenib	YBX1	Unknown	2020	(54)
	hsa_circ_0004277↑	Promotes proliferation, migration and EMT	ZO-1	ExoQuick exosome precipitation solution (System Biosciences, Inc.)	2020	(55)
	hsa_circ_0061395↑	Promotes proliferation	miR-877-5p/PIK3R3	ExoQuick exosome precipitation solution (System Biosciences, Inc.)	2021	(56)
	circRNA-ZNF652↑	Promotes proliferation, migration and invasion	miR-29a-3p/GUCD1	ExoQuick precipitation kit (System Biosciences, Inc.)	2020	(57)
	circCMTM3↑	Promotes tumorigenesis and angiogenesis	miR-3619-5p/SOX9	Exoquick Exosome Precipitation Kit (System Biosciences, Inc.)	2021	(58)
	has_circ_0039411↑	Promotes migration	MMP2	Ultracentrifugation	2020	(59)
	circPTGR1↑	Promotes migration and invasion	miR449a-MET	ExoQuick-TC exosome precipitation solution (System Biosciences, Inc.)	2019	(60)
	hsa_circ_0051443↑	Promotes apoptosis	miR-331-3p	ExoQuick exosome precipitation solution (System Biosciences, Inc.)	2020	(61)
	circANTXR1↑	Promotes proliferation, migration and invasion	miR-532-5p/XRCC5	MagCapture™ Exosome Isolation Kit PS (FUJIFILM Wako Pure Chemical Corporation)	2021	(62)
Protein	ANGPT2↑	Promotes angiogenesis	AKT/eNOS or AKT/ $\beta$ -catenin	Ultracentrifugation	2020	(26)
	CLEC3B↓	Promotes migration, invasion and EMT of HCC cells and ECs	AMPK	ExoQuick-TC™ Exosome Precipitation Solution (System Biosciences, Inc.)	2019	(63)
	VASN↑	Promote proliferation and metastasis	TGF- $\beta$	ExoQuick-TC™ Exosome Precipitation	2015	(64)

				Solution (System Biosciences, Inc.)		
	p120-catenin↑	Suppresses proliferation and metastasis	STAT3	Ultracentrifugation	2019	(65)
	CXCR4↑	Promotes migration, invasion and lymphangiogenesis	MMPs	ExoQuick-TC™ (System Biosciences, Inc.)	2018	(66)
	SMO↑	Promotes proliferation, migration, invasion and EMT	Hedgehog	Ultracentrifugation	2021	(67)
	SMAD3↑	Increases adhesive ability of HCC cells and promote metastasis	PTDEs/ROS	ExoQuick-TC™ (System Biosciences, Inc.)	2018	(68)

<sup>a</sup>Please see the main manuscript for the references. Upward arrows (↑) indicate upregulation and downward arrows (↓) indicate downregulation. HCC, hepatocellular carcinoma; NK, natural killer; EMT, epithelial-mesenchymal transition; ECs, endothelial cells; PTEN, phosphatase and tensin homolog; ERG, erythroblast transformation-specific-related gene; PI3K, phosphatidylinositol-3-kinase; ERK, extracellular regulated protein kinases; HBGF-5, fibroblast growth factor 5; TIMP2, metalloproteinase inhibitor 2; TP53INP1, tumor protein p53 inducible nuclear protein 1; CDKN1A, cyclin-dependent kinase inhibitor 1A; SMEK1, suppressor of mitogen-activated protein kinase kinase 1; TCF21, transcription factor 21; HHIP, hedgehog-interacting protein; EAG1, ether a go go potassium channel 1; VEGFA, vascular endothelial growth factor A; TGFBR3, transforming growth factor β receptor III; VE-Cad/ p120/ ZO-1, VE-Cadherin/ p120-catenin/ zonula occludens 1; PBX3, pre-B-cell leukemia transcription factor 3; CDK2, cyclin-dependent kinase 2; NF-κB, nuclear factor kappa-B; TGF-β, transforming growth factor-β; PCED1B-AS1, PC-esterase domain containing 1B antisense RNA 1; PD-Ls, programmed cell death protein 1 ligands; DLX6-AS1, distal-less homeobox 6 antisense 1; CXCL17, C-X-C motif chemokine ligand 17; ROCK, rho-associated coiled-coil containing kinase; SENP3, SUMO-specific protease 3; EIF4A1, eukaryotic translation initiation factor 4A1; ZFP36, zinc finger protein 36; lncRNA ROR, long noncoding RNA regulator of reprogramming; UHRF1, ubiquitin like with PHD and ring finger domains 1; TIM-3, T cell immunoglobulin and mucin domain 3; circRNA SORE, circular RNA upregulated in sorafenib-resistant HCC cells; YBX1, Y-box binding protein 1; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; GUCD1, guanylyl cyclase domain containing 1; CMTM3, CKLF-like MARVEL transmembrane domain-containing 3; MMP2, matrix metalloproteinase 2; PTGR1, prostaglandin reductase 1; MET, mesenchymal-epithelial transition factor; ANTXR1, anthrax toxin receptor 1; XRCC5, X-ray repair cross-complementing protein 5; eNOS, endothelial nitric oxide synthase; CLEC3B, C-type lectin domain family 3 member B; AMPK, AMP-activated protein kinase; VASN, Vasorin; STAT, signal transducer

and activator of transcription; CXCR4, CXC chemokine receptor-4; SMO, smoothened; SMAD4, mothers against decapentaplegic homolog 4; PTDEs, primary tumor-derived exosomes; ROS, reactive oxygen species.