



# Advances in the Study of CircRNAs in Tumor Drug Resistance

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Recent studies have revealed that circRNAs can affect tumor DNA damage and repair, apoptosis, proliferation, and invasion and influence the transport of intratumor substances by acting as miRNA sponges and transcriptional regulators and binding to proteins in a variety of ways. However, research on the role of circRNAs in cancer radiotherapy and chemoresistance is still in its early stages. Chemotherapy is a common approach to oncology treatment, but the development of tumor resistance limits the overall clinical efficacy of chemotherapy for cancer patients. The current study suggests that circRNAs have a facilitative or inhibitory effect on the development of resistance to conventional chemotherapy in a variety of tumors, suggesting that circRNAs may serve as a new direction for the study of antitumor drug resistance. In this review, we will briefly discuss the biological features of circRNAs and summarize the recent progression of the involvement of circRNAs in the development and pathogenesis of cancer chemoresistance.

**Keywords:** circRNA, tumor chemotherapy, drug resistance, therapeutic target, cancer biology

## BACKGROUND

Circular RNA was first found in plant viroid (1), yeast mitochondrial RNA (2). Unlike linear RNA with 5' cap and 3' tail as terminals, circular RNA is characterized by a covalently closed loop structure with neither 5' to 3' polarity nor polyadenylate tail. This inherent feature led to the widespread underestimation of circular RNA in previous polyadenylated transcriptome analysis. With the advent of specific biochemical and stoichiometric methods, a large number of circular RNA formed by reverse splicing of exons have been found in different cell lines and different species (3). Among them, circular RNA (circRNA), along with their modifiers, have been investigated to play key roles in regulating tumor development and mediating therapy resistance within various cancers, such as hepatocellular carcinoma, breast cancer, lung cancer, gastric cancer, etc. First, almost all of the reported circRNA functions through four classic mechanisms, including: 1, miRNA sponge mechanisms 2, sponging of RBPs (RNA-binding proteins) 3, regulation of transcription 4, translation into peptides or proteins. In addition, two limitations regarding the generation of tumor drug resistance are raised. First, the existing reports on circRNAs in cancer chemoresistance are limited to a few classical drugs and a few types of cancers. Second, most reported circRNAs, limited to those identified in cancer, remain unstudied in the context of the cancer therapeutic response, particularly radioresistance, and numerous unidentified circRNAs remain to be studied. As these limitations are gradually overcome, potential interventions targeting circRNAs are expected to

overcome cancer resistance to radiation and chemotherapy (4, 5). We searched for “circRNA”, “cancer” and “drug resistance” in Pubmed, and obtained a total of 351 relevant papers, and then identified the papers that fit the topic of this paper by preliminary screening of these 351 papers, and the results were 158. According to recent studies, circRNAs mainly (1) upregulate drug efflux transporters or downregulate influx channels, (2) enhance epithelial-mesenchymal transition (EMT) and stemness, (3) alter the copy number of target genes and activation of bypass pathways or downstream signaling, (4) alter endoplasmic reticulum stress, autophagy and phagocytosis, (5) enhance or inhibit DNA repair, (6) impact the tumor microenvironment. Other factors may induce tumor drug resistance but will not be discussed here (4). In this paper, we review the possible tumor drug resistance mechanisms associated with circRNAs and their research progress in the context of chemoresistance by categorizing and summarizing a large number of relevant studies. It also discussed the limitations of available knowledge and future potential directions. The statistics are shown in **Figure 1** and **Table 1**.

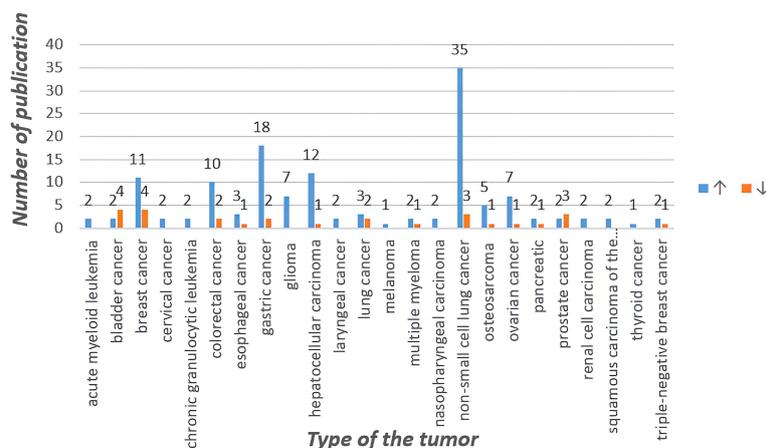
## CircRNAs REGULATE TUMOR DRUG RESISTANCE BY AFFECTING INTRATUMOR DRUG CONCENTRATIONS

It has been shown that reduced drug concentration is the main cause of drug resistance. This may be due to drug segregation in intracellular vesicles and compartments, increased drug efflux or decreased drug influx. These changes may be due to the remodeling of drug channels and transporters, which broadly include ATP-binding cassette (ABC) family proteins, solute carriers, and volume-regulated anion channels (VRACs). M Saxena et al. mechanistically demonstrated that the promoters of ABC transporter proteins carry binding sites for several EMT-inducible transcription factors and that EMT-related transcription factors, such as Twist, Snail, and FOXC2, and

overexpression of these transcription factors increased the promoter activity of ABC transporter proteins. Furthermore, chromatin immunoprecipitation studies showed that Twist binds directly to the E-box element of the ABC transporter protein. EMT inducers were therefore identified as novel regulators of ABC transporter proteins, thus providing a long-term link between aggressiveness and multidrug resistance. Thus, targeting EMT transcription factors could serve as a novel strategy to inhibit tumor metastasis and associated drug resistance (168–171).

According to current reports, circRNAs can increase drug resistance in tumor cells by targeting miRNAs and down-regulating the expression of genes related to drug concentrations in tumors accordingly. For example, in glioma tissues and cell lines, circRNA CEP128 expression was upregulated, and circRNA CEP128 expression was higher in temozolomide-resistant glioma cells than in their parental cells. In contrast, downregulation of circRNA CEP128 inhibited glioma cell proliferation and reduced temozolomide resistance by decreasing the expression of ATP-binding cassette G superfamily member 2 (ABCG2). In addition, miR-145-5p was expressed at low levels in glioma cells and temozolomide-resistant glioma cells, and miR-145-5p was also identified as a target of circRNA CEP128. miR-145-5p overexpression inhibited the proliferation of U251/temozolomide cells and decreased the expression of ATP-binding cassette superfamily member 2, and circRNA CEP128 overexpression blocked these changes (91).

The mRNA and protein levels of ATP-binding cassette transporter protein G2 (ABCG2) were elevated in myeloma adriamycin chemotherapy-resistant cells. Silencing hsa\_circ\_0007841 in resistant cells reduces the mRNA and protein levels of ABCG2, and re-expression of hsa\_circ\_0007841 blocks this reduction. Similarly, overexpression of hsa\_circ\_0007841 effectively upregulated mRNA and protein levels of ABCG2. Inhibition of ABCG2 blocked hsa\_circ\_0007841 overexpression-induced cellular chemoresistance. In addition, ABCG2 reduced the difference in the half-maximal inhibitory concentration between



**FIGURE 1** | Statistics of circRNA related to chemotherapy resistance in different tumors in recent five years.

**TABLE 1 |** CircRNAs in tumor drug resistance.

Name of the tumor	CircRNA	Target(s)	Drugs	Alteration	References	
nasopharyngeal carcinoma	hsa_circ_0002346	miR-422a, FOXQ1 protein	Docetaxel	↑	(6)	
	hsa_circ_0004771	miR-515-5p, IL-25	DDP	↑	(7)	
colorectal cancer	hsa_circ_0005963	miR-122, pyruvate kinase M2 isoform	OXA	↑	(8)	
	hsa_circ_0001451	miR-18b-5p	OXA	↓	(9)	
	hsa_circ_0084443	miR375, FOXM1 protein, Wnt/β-catenin pathway	5-Fu	↑	(10)	
	hsa_circ_0000598	miR-340, the BMI1 protein	Irinotecan	↑	(11)	
	hsa_circ_0032833	miR-125-5p, MSI1 protein	OXA	↑	(12)	
	hsa_circ_0071589	miR-526b-3p, KLF12 protein	DDP	↑	(13)	
	hsa_circ_0001806	miR-944, FZD7 protein	DOX	↑	(14)	
	hsa_circ_0002211	miR-31-5p, KANK1 protein	5-Fu	↓	(15)	
	hsa_circ_0007031	miR-133b, the ABCC5 protein	5-Fu	↑	(16)	
	hsa_circ_0000338	miR-217, miR-485-3p	5-Fu	↑	(17)	
	hsa_circ_0020095	miR-487a-3p, SOX9 protein	DDP	↑	(18)	
	multiple myeloma	hsa_circ_0007841	<i>ABCG2</i>	DOX	↑	(19)
		hsa_circ_0001141	miR-615-3p, PRKCD protein	BTZ	↓	(20)
	non-small cell lung cancer	hsa_circ_0007841	miR-129-5p, JAG1 protein	BTZ	↑	(21)
		hsa_circ_0007385	miR-519D-3p, <i>HMGB1</i>	DDP	↑	(22)
hsa_circ_103809		miR-377-3p, <i>GOT1</i>	DDP	↑	(23)	
hsa_circ_0084003		miR-381-3p, CXCR4 protein	Anti-PD1	↑	(24)	
hsa_circ_0082374		miRNA let-7, <i>PD-L1</i>	Anti-PD1	↑	(25)	
hsa_circ_0031250		miR-4458, <i>REV3L</i>	DDP	↑	(26)	
hsa_circ_0096157		P21 protein, <i>CDK4-cyclin D1</i> , <i>Bcl-2</i>	DDP	↑	(27)	
hsa_circ_0004015		miR-1183, <i>PDPK1</i>	TKI	↑	(28)	
hsa_circ_0085131		miR-654-5p, <i>ATG7</i>	DDP	↑	(29)	
hsa_circ_0000079		FXR1 protein	DDP	↓	(30)	
hsa_circ_0076305		miR-296-5p, STAT3 protein	DDP	↑	(31)	
hsa_circ_0002483		miR-182-5p, GRB2 protein, FOXO1 protein, FOXO3 protein	PTX	↓	(32)	
hsa_circ_0002130		miR-498, <i>GLUT1</i> , <i>HK2</i> , <i>LDHA</i>	Osimertinib	↑	(33)	
hsa_circ_0011292		miR-379-5p, TRIM65 protein	PTX	↑	(34)	
hsa_circ_0014235		miR-520a-5p, <i>CDK4</i>	DDP	↑	(35)	
circMTDH.4		miR-630, <i>AEG-1</i>	5-Fu	↑	(36)	
hsa_circ_102481		miR-30a-5p, ROR1 protein	TKI	↑	(37)	
hsa_circ_0023303		miR-187-3p, FGF9 protein	DDP	↑	(38)	
hsa_circ_0003998		miR-136-5p, CORO1C protein	DTX	↑	(39)	
hsa_circ_0008928		miR-488, HK2 protein	DDP	↑	(40)	
hsa_circ_0005909	miR-338-3p, SOX4 protein	ADM	↑	(41)		
hsa_circ_103615	<i>ABCB1</i>	DDP	↑	(42)		
hsa_circ_0072083	miR-195-5p, KPNA4 protein	PTX	↑	(43)		
hsa_circ_0014130	miR-493-5p, ROCK1 protein	DDP	↑	(44)		
circASXL1	miR-206	DDP	↑	(45)		
hsa_circ_0006404	miR-543, FOXO3 protein	DDP	↓	(46)		
hsa_circ_0003222	miR-527, PHF21B protein, Wnt/β-catenin pathway	Anti-PD1	↑	(47)		
hsa_circ_0002874	miR-1273f, MDM2 protein, p53 protein	PTX	↑	(48)		
hsa_circ_0001658	miR-409-3p, TWIST1 protein	Gefitinib	↑	(49)		
circPRMT5	miR-138-5p, <i>MYH9</i>	DDP	↑	(50)		
hsa_circ_0076305	miR-186-5p, <i>ABCC1</i>	DDP	↑	(51)		
hsa_circ_0014130	miR-101, <i>ABCC1</i>	DDP	↑	(52)		
hsa_circ_0005152	miR-934, SHP2 protein	Anti-PD1	↑	(53)		
hsa_circ_0014130	miR-545-3p, YAP1 protein	DTX	↑	(54)		
hsa_circ_0023404	miR-646, SOX4 protein	DDP	↑	(55)		
hsa_circ_0001821	miR-526-5p, GRK5 protein	PTX	↑	(56)		
hsa_circ_0031608	miR-137, <i>CXCL12</i>	DDP	↑	(57)		
hsa_circ_0079587	miR-328-3p, miR-3173-5p, PKP3 protein	Anti-PD1	↑	(58)		
hsa_circ_100565	miR-337-3p, ADAM28 protein	DDP	↑	(59)		
lung cancer	hsa_circ_0000199	miR-516b-5p, STAT3 protein	DDP	↑	(60)	
	hsa_circ_0030998	miR-558, MMP1 protein, MMP17 protein	PTX	↓	(61)	
	hsa_circ_0008717	miR-556-3p, AK4 protein	DDP	↑	(62)	
	hsa_circ_0001821	miR-145-5p, <i>ABCC1</i> protein	DDP	↑	(63)	
	hsa_circ_0007798	ASK1 protein	Gefitinib	↓	(64)	
hepatocellular carcinoma	hsa_circ_0082002	miR-30-5p, <i>Snail</i> , DPP4 protein, <i>CXCL10</i>	Anti-PD1	↑	(65)	
	hsa_circ_0048677	miR-449c-5p, TIM-3 protein	Anti-PD1	↑	(66)	
	hsa_circ_0087293	miR-103a-2-5p, miR-660-3p, Wnt/β-catenin pathway	Sorafenib	↑	(67)	

(Continued)

TABLE 1 | Continued

Name of the tumor	CircRNA	Target(s)	Drugs	Alteration	References
	hsa_circ_0001001	miR-605, FOXO3 protein, ABCB1 protein	OXA	↑	(68)
	hsa_circ_0087293	YBX1 protein	Sorafenib	↑	(69)
	hsa_circ_0104670	miR-155-5p, PDK1 protein	DDP	↑	(70)
	hsa_circ_0031242	miR-924, POU3F2 protein	DDP	↑	(71)
	hsa_circ_G004213	miR-513b-5p, PRPF39 protein	DDP	↓	(72)
	hsa_circ_0025039	miR-1324, MECP2 protein	Sorafenib	↑	(73)
	hsa_circ_0006404	miR-199a-5p, ABCC1 protein	ADM	↑	(74)
	hsa_circ_0003998	miR-218-5p, <i>EIF5A2</i>	ADM	↑	(75)
	hsa_circ_0000384	miR-148a, STX3 protein, PTEN protein	DDP	↑	(76)
cervical cancer	hsa_circ_0007874	miR-6893, S100A1 protein	DDP	↑	(77)
	hsa_circ_0023404	miR-5047, VEGFA protein	DDP	↑	(78)
osteosarcoma	hsa_circ_0000073	miR-145-5p, miR-151-3p, NRAS protein	MTX	↑	(79)
	hsa_circ_0001821	ABCB1 protein	ADM	↑	(80)
	hsa_circ_0003496	miR-506-3p, SEMA6D protein, Wnt/β-catenin pathway	DDP	↑	(81)
	hsa_circ_0001141	miR-524, RASSF6 protein	ADM	↓	(82)
	hsa_circ_0081001	miR-494-3p, TGM2 protein	MTX	↑	(83)
	hsa_circ_0005986	miR-760, <i>EZH2</i>	DXR	↑	(84)
melanoma	hsa_circ_0020710	miR-370-3p, <i>CXCL12</i>	Anti-PD1	↑	(85)
laryngeal cancer	hsa_circ_0004507	miR-873	DDP	↑	(86)
	hsa_circ_0019340	miR-376a, ATG2A protein	DDP	↑	(87)
acute myeloid leukemia	circPAN3	Beclin1, p62, AMPK/mTOR pathway	ADM	↑	(88)
	circPAN3	miR-153-5p, miR-183-5p, XIAP protein	ADM	↑	(89)
thyroid cancer	hsa_circ_0060060	miR-144-3p, <i>TGF-α</i>	DDP	↑	(90)
glioma	hsa_circ_0102722	miR-145-5p, ABCG2 protein	TMZ	↑	(91)
	hsa_circ_0005660	miR-132	TMZ	↑	(92)
	hsa_circ_0000284	miR-421, ZIC5 protein	TMZ	↑	(93)
	hsa_circ_0000284	miR-524-5p, KIF2A protein, PI3K/AKT pathway	TMZ	↑	(94)
	hsa_circ_0072083	miR-1252-5p, ALKBH5 protein, NANOG protein	TMZ	↑	(95)
	hsa_circ_0002330	miR-502-5p, NRAS/MEK1/ERK1-2 signal	TMZ	↑	(96)
	hsa_circ_0005198	miR-198, TRIM14 protein	TMZ	↑	(97)
squamous carcinoma of the oral cavity	hsa_circ_0109291	miR-188-3p, ABCB1 protein	DDP	↑	(98)
	hsa_circ_0011946	miR-338-3p, Lin28B protein	DDP	↑	(99)
ovarian cancer	hsa_circ_0001946	miR-1270, the SCAI factor	DDP	↓	(100)
	hsa_circ_0001741	miR-1299, NEK2 protein	PTX	↑	(101)
	hsa_circ_0000714	miR-370-3p, CDK6 protein, RB protein, RAB17 protein	PTX	↑	(102)
	hsa_circ_0063809	miR-1252, FOXR2 protein	PTX	↑	(103)
	hsa_circ_0008234	miR-22, miR-150-3p, <i>CEBPG</i> , <i>FMNL3</i>	DDP	↑	(104)
	hsa_circ_0002711	miR-211-5p, HOXC8 protein	PTX	↑	(105)
	hsa_circ_0001756	miR-338-3p, CHTOP protein	DDP	↑	(106)
	hsa_circ_0063809	miR-149-5p, SIK2 protein	PTX	↑	(107)
chronic granulocytic leukemia	hsa_circ_0080145	miR-326, PPF1A1 protein	IM	↑	(108)
	hsa_circ_0009910	miR-34a-5p, ULK1 protein	IM	↑	(109)
bladder cancer	hsa_circ_0000284		GEM	↓	(110)
	hsa_circ_103809	miR-516a-5p, FBXL18 protein	GEM	↑	(111)
	hsa_circ_0001785		DDP	↑	(112)
	hsa_circ_0000285		DDP	↓	(113)
	hsa_circ_0072309	MutSα, ATM, p73 protein	DDP	↓	(114)
	hsa_circ_0008399	WTAP protein	DDP	↓	(115)
prostate cancer	hsa_circ_0006404		DTX	↓	(116)
	hsa_circ_0001427	miR-181c-5p, ARv7 protein	Enz	↓	(117)
	hsa_circ_0000735	miR-7	DTX	↑	(118)
	hsa_circ_0001141	miR-17, Wnt/β-catenin pathway, PI3K/AKT/mTOR pathway	Enz	↓	(119)
	hsa_circ_0005276	miR-1182, TPD52 protein	DTX	↑	(120)
breast cancer	hsa_circ_0025202	miR-197-3p, HIPK3 protein	TAM	↓	(121)
	hsa_circ_0025202	miR-182-5p, FOXO3a protein	TAM	↓	(122)
	hsa_circ_0001839	miR-548p, the PBLD protein	ADM	↓	(123)
	hsa_circ_007874	EG5 protein, TRAF4 protein	Monastrol	↓	(124)
	hsa_circ_0008717	let-7a-5p, the DUSP7 protein	PTX	↑	(125)
	hsa_circ_0001946	miR-7, CCNE1 protein	5-Fu	↑	(126)
	circ-RNF111	miR-140-5p, transcription factor E2F3	PTX	↑	(127)
	hsa_circ_0001667	miR-4458, NCOA3 protein	ADM	↑	(128)
	hsa_circ_0125597	miR-216b, <i>HMG2A</i>	5-Fu	↑	(129)

(Continued)

TABLE 1 | Continued

Name of the tumor	CircRNA	Target(s)	Drugs	Alteration	References
	hsa_circ_0001461	miR-525-5p, SKA1 subunit	OXA	↑	(130)
	hsa_circ_0006528	miR-1236-3p, CHD4 protein	ADM	↑	(131)
	hsa_circ_0062558	miR-153-5p, ANLN protein	Lapatinib	↑	(132)
	hsa_circ_0085495	miR-873-5p, integrin $\beta$ 1	ADM	↑	(133)
	hsa_circ_0001598	miR-1184, <i>PD-L1</i>	Trastuzumab	↑	(134)
	circ_UBE2D2	miR-200a-3p	TAM	↑	(135)
triple-negative breast cancer	hsa_circ_0005728	miR-512-3p, CDCA3 protein	ADM	↓	(136)
	hsa_circ_0007503	miR-142, WWP1 protein, PI3K/AKT pathway	PTX	↑	(137)
	hsa_circ_005239	miR-361-5p, TLR4 protein	PTX	↑	(138)
renal cell carcinoma	hsa_circ_0035483	hsa-miR-335, <i>CCNB1</i>	GEM	↑	(139)
	hsa_circ_0031608	miR-1184, GPCPD1 protein	Sunitinib	↑	(140)
esophageal cancer	hsa_circ_001275	miR-370-3p, WNT7a protein	DDP	↑	(141)
	hsa_circ_0006168	miR-194-5p, JMJD1C protein	PTX	↑	(142)
	circPSMC3	miR-10a-5p, PTEN protein	Gefitinib	↓	(143)
	hsa_circ_0000337	miR-377-3p, JAK2 protein	DDP	↑	(144)
gastric cancer	hsa_circ_0026359	miR-1200, the POLD4 protein	DDP	↑	(145)
	hsa_circ_0006990	miR-125b-5p, STAT3 protein	DDP	↑	(146)
	hsa_circ_0032821	miR-515-5p, SOX9 protein	OXA	↑	(147)
	hsa_circ_0000234	miR-142-3p, ROCK2 protein	DDP	↑	(148)
	hsa_circ_0058147	miR-182-5p	DDP	↑	(149)
	hsa_circ_0001313	miR-618, BCL2 protein	DDP	↑	(150)
	hsa_circ_0000199	miR-198, PIK3R1 protein, p85 $\alpha$ protein, PI3K/AKT pathway	DDP	↑	(151)
	hsa_circ_0000657	miR-99a-5p, the MTMR3 protein	DDP	↓	(152)
	hsa_circ_0001821	miR-124-3p, ZEB1 protein	PTX	↑	(153)
	hsa_circ_0004771	miRNA-138-5p, HIF-1 $\alpha$ factor	5-Fu	↑	(154)
	hsa_circ_0006089	miR-330-3p, NT5E protein	DDP	↑	(155)
	hsa_circ_0004339	miR-802, <i>BMI1</i>	DDP	↑	(156)
	circ MTHFD2	miR-124, <i>MDR-1</i>	MTA	↑	(157)
	hsa_circ_0001546	miRNA-421, ATM/CHK2/P53 pathway	OXA	↓	(158)
	hsa_circ_0031452	miR-137, PBX3 protein	DB	↑	(159)
	hsa_circ_0000144	miR-502-5p, ADAM9 protein	OXA	↑	(160)
	hsa_circ_0000260	miR-129-5p, MMP11 protein	DDP	↑	(161)
	hsa_circ_0001821	miR-152-3p, HDGF/PI3K/AKT pathway	DDP	↑	(162)
	hsa_circ_0001821	miR-30a-5p, YAP1 protein	DDP	↑	(163)
	hsa_circ_0002570	miR-490-3p, HMGA2 protein, HNRNPk protein, $\beta$ -catenin	DDP	↑	(164)
pancreatic	hsa_circ_0000284	miR-330-5p, RASSF1 protein	GEM	↑	(165)
	hsa_circ_0013587	miR-1227, E-Cadherin	Erlotinib	↓	(166)
	hsa_circ_0030167	miR-338-5p, Wif1, Wnt8, $\beta$ -catenin	GEM	↑	(167)

↑ means increased; ↓ means decreased.

parental and resistant cells. These findings suggest that hsa\_circ\_0007841 can promote a pattern of acquired chemoresistance in myeloma cells through the upregulation of ABCG2, providing a new molecular basis for chemotherapy in multiple myeloma (19).

In laryngeal cancer, knockdown of circ\_0004507 reduces the protein levels of multidrug resistance-associated protein-1 (MRP1) and multidrug resistance gene 1 (*MDR1*), which are associated with cellular cassette transporters and confer multidrug resistance to tumor cells by reducing the uptake of anticancer drugs (86).

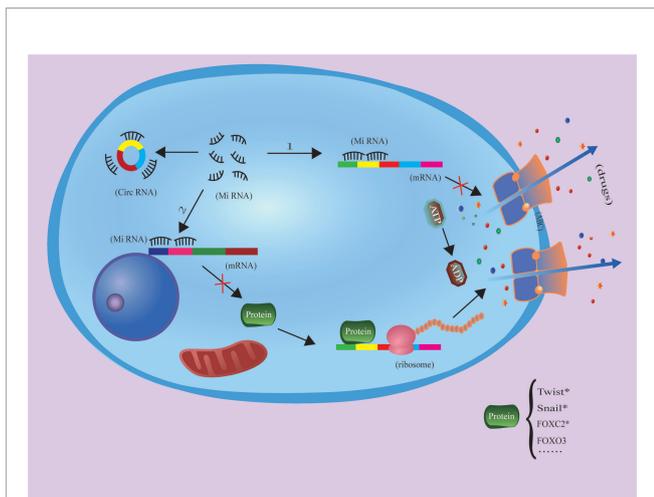
In hepatocellular carcinoma, circRNA PTGR1 regulates drug resistance to 5-fluorouracil (5-FU) and the growth tumor cells by regulating the miR-129-5p/ABCC1 axis (172). Additionally, studies of adriamycin resistance in hepatocellular carcinoma have shown that circFOXO3 promotes resistance to adriamycin in by regulating the miR-199a-5p/ATP binding cassette C family member 1 axis (74). However, circRNA circFBXO11 regulates hepatocellular carcinoma progression and oxaliplatin resistance through the

miR-605/FOXO3/ABCB1 axis (68), so further study is needed determine whether circFBXO11 regulates circFOXO3 and its downstream signaling through this axis (Figure 2).

It can be seen that the effect of circRNA on ABC transporter protein is important and diverse in each type of tumor, but there are various factors that affect the concentration of drugs in tumor cells, and ABC transporter protein is only one of the drug channels. However, it is worth thinking why circRNA are mostly reported to regulate ABC transporter protein.

## CircRNAs ENHANCE EMT AND STEMNESS

Briefly, EMT is an epigenetic program by which cells lose their epithelial phenotype and acquire mesenchymal features. Common EMT-inducible transcription factors, such as twist and snail, which contain complementary binding sites, act as promoters of ABC transporters, and they enhance not only EMT



**FIGURE 2** | CircRNAs inhibit miRNA function through the molecular sponging mechanism, increasing ABC expression and drug efflux to increase tumor cell drug resistance. The protein with \* has been proven to be an ABC-related transcription factor, but there is no literature to prove that it is regulated by circRNA.

but also ABC transporter expression (4, 171). In recent years, it has been shown that circRNAs can influence tumor cell resistance by enhancing EMT; for example, circ\_001680 and circ-NOTCH1 are elevated in colorectal cancer (CRC) and gastric cancer (GC), respectively, and both these circRNAs can promote cancer stem cell (CSC) expansion *via* EMT (11, 173). Chen et al. showed that failure to eradicate cancer cells that acquire stem cell features through EMT activation or senescence is another reason for impaired cancer treatment outcomes (174–177). Second, CSCs are able to remain dormant for a long period of time to escape harmful stresses such as radiotherapy and chemotherapy. Once harmful stress is lifted, CSCs can differentiate, proliferate or metastasize at the primary lesion and subsequently invade other organs, leading to tumor recurrence or metastasis (178, 179). For example, circFOXO3 reduction promotes prostate cancer progression and doxorubicin resistance. circFOXO3 inhibits prostate cancer cell survival, migration, invasion, and doxorubicin resistance, which is associated with circFOXO3-mediated inhibition of Foxo3 and EMT (116).

Nithila A. Joseph et al. showed that in lung adenocarcinoma cells, circRNA CCDC66 increases SUMOylation modifications related to the HGF-MET signaling pathway and epidermal growth factor receptor (EGFR)-controlled SAE2 through association with EMT and thus affects the resistance of tumor cells to tyrosine kinase inhibitors (TKIs) targeting EGFR (180). Among them, SAE2 is one of the subunits of SUMO-activating enzyme E1, and SUMO-mediated modifications have been shown to be importantly associated with the proliferation, migration and invasion of a variety of tumors (181, 182). We found that circRNA CCDC66 has been reported to be associated with mechanisms of chemoresistance generation not only in lung adenocarcinoma cells but also in gastrointestinal tumors; for example, DHX9 phosphorylation induced by oxaliplatin

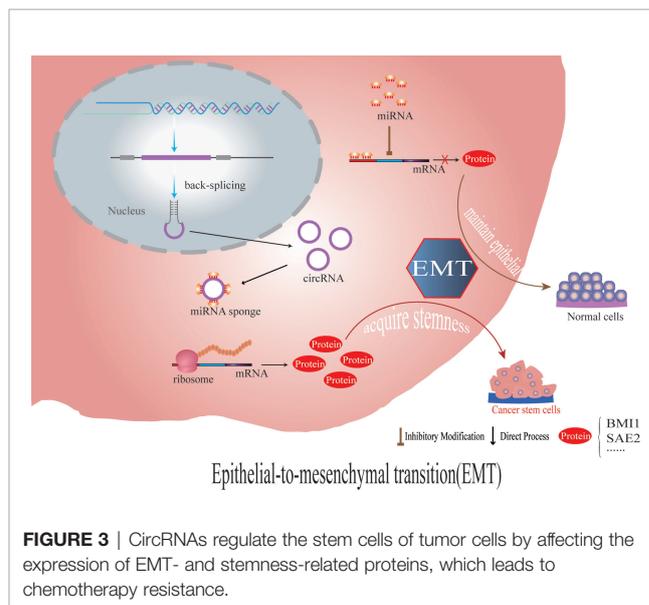
chemotherapy in colorectal cancer promotes the expression of oncogenic circRNA CCDC66 to affect chemoresistance (183), and circRNA CCDC66 in gastric cancer through the miR-618/BCL2 axis regulates cisplatin resistance in gastric cancer (150). More data is needed to assess the resistance induced by different mechanisms of different drugs yet related to the same circRNA (Figure 3).

It is thus clear that circRNA also has an important role in the regulation of EMT and stemness. However, EMT and stemness is different from the regulation of drug channel proteins, and changes often imply an all-round overall effect in EMT and stemness. Therefore, it is clear that since circRNA can enhance drug resistance by regulating EMT and stemness, circRNA must have other regulatory functions while enhancing EMT and stemness. In short, the effect of circRNA on tumors, too, is holistic. For example, the circ-CPA4 regulated cell growth, mobility, stemness and drug resistance in NSCLC cells and inactivated CD8 T cells in the tumor immune microenvironment (25).

### CircRNAs ALTER THE COPY NUMBER OF TARGET GENES AND ACTIVATE BYPASS PATHWAYS OR DOWNSTREAM SIGNALING

#### CircRNAs Compete for Endogenous MiRNAs

CircRNAs competitively bind miRNAs (184, 185), so as to serve as intracellular competitive endogenous RNA, suppressing the effects of miRNAs on target genes. For example, the circRNA AKT3 enhances cisplatin resistance in gastric cancer by inhibiting miR-198 and upregulating PIK3R1, which was experimentally shown to be a downstream molecule of miR-198 (151). PIK3R1 encodes a regulatory subunit of PI3K and has a role in positively regulating the PI3K signaling pathway.



**FIGURE 3** | CircRNAs regulate the stem cells of tumor cells by affecting the expression of EMT- and stemness-related proteins, which leads to chemotherapy resistance.

The autophagic process also requires phosphatidylinositol 3-phosphate (PI3P), and the inhibition of PI3P can inhibit the formation of autophagic vesicles. Whether PI3K can affect tumor cell drug resistance through the regulation of autophagy deserves further study.

In addition, some studies have shown that circRNA can promote its own loop and form positive feedback by up-regulating the expression of downstream transcription factors. For example, in gastric cancer, circFAM73A increases the expression of HMG (high mobility group) A2 through miR-490-3p, HMGA2 plays a dichotomous role in regulating circFAM73A expression, i.e., HMGA2 facilitates the transcriptional activation of FAM73A by E2F1 and elevates the efficiency of circFAM73A circularization by HNRNPL, HMGA2 promotes stem cell-like properties and cell malignancy in GC cells (164). It is worth considering whether this process of positive feedback loops to improve tumor drug resistance is common. With regard to circRNA and its sponge miRNA, through a large number of literature review and summary, we find that there is often more than one miRNA combined with each other under the same circRNA. For example, also in non-small cell lung cancer, circRNAPRMT5 can target miR-381-3p (24) and miR-4458 (26) to regulate the expression of different downstream proteins to promote tumor, and the same circ\_007630 can also target miR-296-5p (31) and miR-186-5p (51) respectively. Interestingly, the same miRNA targets different genes in different tumors and regulates downstream pathways, such as miR-338-3p, which promotes the progressive drug resistance of oral squamous cell carcinoma (99) and ovarian cancer (106) at the same time. As we all know, the effect of circRNA on tumor drug resistance is often the result of a variety of mechanisms, so we need to pay attention to the interaction between various mechanisms and pathways, and pay attention to the integration and analysis of various mechanism information. The coincidence targets in these different pathways provide some support for us to analyze the generation of drug resistance of tumor cells as a whole. For example, miR-338-3p can play a role in promoting drug resistance in a variety of tumors according to current reports (99, 106), but the mechanisms of action are different. It is worth thinking whether the regulatory mechanisms of the same miRNAs in different tumor lines overlap, and if not, what determines the target of miRNAs to exert regulatory effects in tumor cells, and if so, whether it is of limited significance to focus on individual pathways according to most of the current literature. Moreover, we found that there are literatures about target overlap at all three levels of circRNA, miRNA and protein (32, 51, 63, 88, 89, 149).

### CircRNAs Function as a Reservoir or a Stabilizing Factor for the MiRNA

Studies have shown that in the progress of chemoresistance of prostate cancer, as circRNA17 is positively correlated with the expression level of miR-181c-5p, this circRNA may not function as a sponge to sequester the miRNAs, but likely function as a reservoir or a stabilizing factor for the miR-181c-5p (117). Mechanistically, speculated the binding of miR-181c-5p with circRNA17 might enhance the miR-181c-5p stability by

repressing its degradation through nucleases such as Tudor-SN endonuclease (186). In addition, this stabilizing effect appears particularly significant *in vivo* during tumor growth and less so in cells grown in tissue culture. The exact details of these phenomena remain to be further determined. CircRNA adsorbs miRNA can prevent the degradation of the latter, which reminds us of the need to add deeper thinking to the traditional study of ceRNA (competing endogenous RNA) mechanism.

### CircRNAs Bind RNA-Binding Proteins

CircRNAs serve as protein baits or antagonists, thus arresting the function of proteins, thereby affecting the related progresses (184). For example: circLIFR synergizes with MSH2 to attenuate chemoresistance *via* MutS $\alpha$ /ATM-p73 axis in bladder cancer (114). In addition, the same circRNA can perform different functions in different cells or in the same cell through different pathways. For example, in hepatocellular carcinoma cells, circRNA-SORE can mediate hepatocellular carcinoma resistance to sorafenib by stabilizing YBX1 (67), while N-6-methyladenosine-modified circRNA-SORE can also maintain hepatocellular carcinoma resistance to sorafenib by regulating  $\beta$ -catenin signalin (69). It should be pointed out that the previously mentioned circRNA-SORE mediates the drug resistance of hepatocellular carcinoma to sorafenib by stabilizing the YBX1 protein; in fact, it does not involve gene copy number and activation, but rather, circRNA directly plays a role in the process of protein stability and degradation. YBX1 is a kind of RNA binding protein (RBP). At present, an increasing number of evidences suggest the direct binding of circRNAs to RBPs. Most of them continue to regulate the expression of downstream signaling pathways by affecting the stability or degradation of target proteins, and there is often more than one downstream pathway involved (30, 124). Although the RBP pathway is different from pathways influenced by circRNA regulation of the target gene, in essence, it continues to play its biological function by regulating the expression (by targeting genes) or degradation (by targeting proteins) of related proteins. It is worth mentioning that there are also reports that circRNA directly binds to the DNA promoter to regulate transcription and thus affect the progression of liver cancer (84, 187).

### CircRNAs Encode Proteins

CircRNAs can translate to proteins through a cap-independent manner (184, 188). Yang et al. demonstrated that N-methyladenosine(m6A) could promote the initiation of protein translation from circRNAs in human cells (189). For example, PengLi et al. found that circMRPS35 not only regulates the STX3-PTEN axis through sponge miR-148A, but also encodes circMRPS35-168aa, resulting in cisplatin resistance, thus playing a carcinogenic role in hepatocellular carcinoma (76). In addition, in gastric cancer, YuZhang et al. found that circDIDO1 inhibits the progression of gastric cancer by encoding a new DIDO1-529aa protein and regulating the stability of PRDX2 protein (190). At present, there are relatively few articles about circRNA affecting tumor chemotherapy resistance by encoding proteins, and in most of these articles, circRNA plays a role in multiple

pathways, For example, even playing the role of molecular sponge also encodes protein, the emergence of this experimental result may be preconceived thinking about the mechanism of circRNA molecular sponge. Whether this preconceived way of thinking limits the study of circRNA multi-mechanism is worthy of further study (Figure 4).

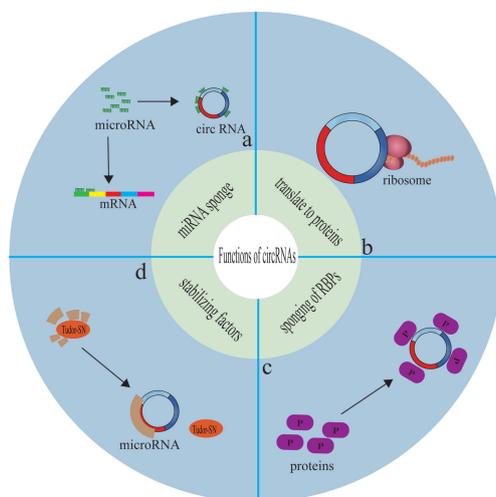
Although this section outlines that circRNAs affect cancer drug resistance through the copy number alteration and activation of downstream genes, circRNA downstream genes are often proto-oncogenes or oncogenes, and the outcomes are mostly achieved by affecting the immune escape of cancer cells and the ability of cancer cells to repair genes or altering autophagy or EMT. For example, in studies of drug resistance in non-small-cell lung cancer (NSCLC), circFGFR1 also promotes NSCLC cell development and immune system escape by sponging miR-381-3p and targeting CXCR4, a gene that has been identified as a key oncogene in several cancers, and knockdown of CXCR4 reverses circFGFR1-induced NSCLC cell proliferation, migration and invasion (24). In addition, circFGFR1 is a sponge for several miRNAs. Additionally, in hepatocellular carcinoma cell resistance-related studies, circMET, can drive hepatocellular carcinoma immunosuppression and anti-PD-1 therapy resistance *via* the miR-30-5p/Snail/DPP4 axis. circMET also induces hepatocarcinogenesis and immune tolerance *via* the Snail/DPP4/CXCL10 axis (65).

The role of circRNAs in tumor drug resistance can be broadly classified into two categories according to their role, and in addition to the drug resistance enhancing effect mentioned above, there are also reports of drug resistance inhibiting effects. CircRNA can be negatively correlated with the generation of tumor drug resistance, For example, circ\_0000079 induces the ribonucleic acid binding protein FXR1 to block the formation of the FXR1/PrCKI complex and reduces its promoting effects on NSCLC cell invasion and cisplatin

resistance; it was shown that circ\_0000079 (CiR79) levels were significantly downregulated in NSCLC patients, especially in cisplatin-resistant NSCLC patients, and that reduced circ\_0000079 levels were significantly associated with overall survival in NSCLC patients. The results of Cell Counting Kit-8 and Transwell cell invasion assays showed that circ\_0000079 overexpression significantly inhibited the proliferation and invasion of cisplatin-resistant NSCLC cells. Functionally and mechanistically, circ\_0000079 negatively regulates the FXR1/PRKCI-mediated phosphorylation of glycogen synthase kinase 3 $\beta$  and activator protein 1, thereby decreasing the protein levels of the *Snail* gene, an important promoter gene that regulates cancer cell growth and EMT (30). This shows that circRNAs may be able to exert opposite effects on the biological behavior of tumor cells through different signaling pathways in different tumor cells.

## CircRNAs REGULATE ENDOPLASMIC RETICULUM STRESS, AUTOPHAGY AND PHAGOCYTOSIS

Both the activation and inhibition of endoplasmic reticulum stress have been shown to attenuate chemo- and radioresistance in tumors (191–193), and endoplasmic reticulum stress is also a potent trigger of autophagy for controlling cancer sensitivity (194). Autophagy is a process by which cells engulf their own cytoplasmic proteins or organelles and encapsulate them into vesicles that fuses with lysosomes to form autophagic lysosomes, which degrade the contents they encapsulate. However, autophagy is also a double-edged sword. Mild autophagy facilitates cell survival under normal or mild stress conditions, while excessive autophagy can lead to cell death. Smith et al.



**FIGURE 4** | Functions of circRNAs. **(A)** circRNAs competitively bind miRNAs, so as to serve as intracellular competitive endogenous RNA, suppressing the effects of miRNAs on target genes. **(B)** circRNAs can translate to proteins through a cap-independent manner. **(C)** circRNAs serve as protein baits or antagonists, thus arresting the function of proteins, thereby affecting the related progresses. **(D)** circRNA function as a reservoir or a stabilizing factor for the miRNA.



that circ\_0026359 is overexpressed and correlated with cisplatin resistance and poor survival in gastric cancer patients, and conversely, deletion of circ\_0026359 enhances miR-1200 activity, which reduces the expression level of POLD4 and thus reduces the resistance of gastric cancer cells to cisplatin. In contrast, POLD4 plays a role in cell proliferation and the maintenance of human cell genome stability. Low expression of POLD4 has been reported to impair DNA repair systems, including nucleotide excision repair, and increase the risk of lung cancer formation (145). As an additional example, in triple-negative breast cancer, hsa\_circ\_0000199 may activate the DNA repair molecule histone family member X (H2AX), leading to cisplatin resistance. This also involves the classical PI3K/AKT pathway (151, 200).

CircRNA AKT3 upregulates PIK3R1 by inhibiting miR-198 to enhance cisplatin resistance (by inhibiting apoptosis and facilitating DNA damage repair) in gastric cancer. Mechanistically, circAKT3 activates the PI3K/AKT signaling pathway in GC cells by sponging miR-198 to eliminate the inhibitory effect of this miRNA on its target gene *PIK3R1*. Activation of the PI3K/AKT pathway contributes to the upregulation of the DNA repair molecule BRCA1, leading to resistance to cisplatin-based chemotherapy. CircAKT3 affected the DNA damage response (DDR) in GC cells, suggested that circAKT3 may enhance cisplatin resistance through the PI3K/AKT pathway and DDR mechanism in GC cells (151). In summary, to study the effect of DNA repair ability on tumor drug resistance, it is crucial to determine the connection between circRNA and DNA damage repair genes or proteins, which are commonly associated with DNA damage repair, such as POLD4, H2AX, BRCA1, etc. In addition, these genes or proteins are often linked to some classical signaling pathways, probably because repair involving DNA requires some well-established and stable genes and pathways.

## CircRNAs REGULATE TUMOR MICROENVIRONMENT (TME)

The TME is a complex ecosystem with microbiota, an acidic pH, inflammatory factors, matrix metalloproteinases, extracellular matrix (ECM), tumor-associated fibroblasts (CAFs), and tumor-associated macrophages (TAMs). The impact of the tumor microenvironment on the tumor is frequent and must be considered, for example, because the TME of the primary tumor and the corresponding metastases differ, which affects the sensitivity of cancer cells (201, 202). It has been demonstrated that external factors such as inflammatory factors, acidity and alkalinity of the microenvironment in which the tumor is located regulate tumor drug resistance by influencing protein synthesis, organelle division, and enzyme function in tumor cells. The TME can both directly and indirectly affect the ability of circRNAs to regulate tumor drug resistance; for example, the inflammatory factor IL-7 can reduce the expression of ABCG2 (ATP-binding cassette family protein) and regulate cisplatin resistance in NSCLC (203). A hypoxic tumor microenvironment can cause excessive mitochondrial division of NK cells, which reduces the

immune surveillance function of the organism (204). Direct regulation of circRNAs is also possible; for example, in a study on the previously mentioned circRNA CCDC66 in lung adenocarcinoma resistance, the expression of SAE2 was mainly regulated by EGFR, whereas the expression of circRNA CCDC66 was positively regulated by FAK and c-Met and negatively regulated by nAChR7 $\alpha$ . The immediate response to hypoxia can increase phosphorylated c-Met and SAE2 expression and EMT (180). This regulates tumor drug resistance upstream from circRNA. It is thus clear that the TME and the role of circRNAs are closely related, and the effect of the TME on tumor drug resistance may bring new ideas and possibilities for the exploration of mechanisms for drug-resistant tumors in circRNA research.

## CircRNAs IN IMMUNE CHECKPOINT INHIBITORS RESISTANCE

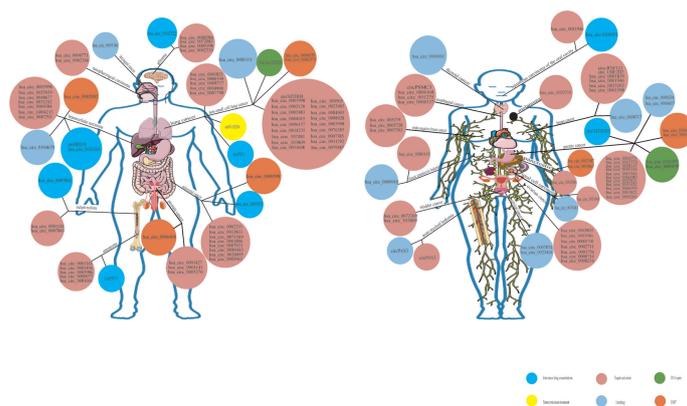
Chemotherapeutic drugs have no specific target, and their effects are all over the body, and they are extremely sensitive to cells that proliferate rapidly. It can inhibit and kill the rapidly proliferating tumor cells, but also inevitably “accidentally” injure the normal cells of human body, which is a simple and brutal anti-cancer method of “Injure the enemy by 1000 and lose 800 by yourself”. In contrast, there are sites on the surface of targeted drugs that can specifically bind to tumor cells, which can precisely identify the lesion site, and when cancer cells are identified by immune checkpoint inhibitors, they are destroyed. The effect on normal cells is minimal. Immune checkpoint inhibitors (ICIs) have been shown to be highly efficient in the treatment of solid tumors. Therefore, ICIs treatment may be an important tool for tumor treatment in the future. However, limited benefit in terms of response and survival has been reported in many patients because of drug resistance. PD-L1 expression remains the only validated marker in clinics, molecular profiling has brought valuable information, showing that the tumor mutation load and microsatellite instability (MSI) status were associated to higher response rates in nearly all cancer types (205). The main immune checkpoint inhibitors currently in clinical use are anti-CTLA-4 and antibodies against PD-1 and its ligand PD-L1, which can be applied to many types of cancer and have shown significant improvements in patient survival time. However, despite the success of ICIs, resistance to these agents restricts the number of patients able to achieve durable responses, and immune-related adverse events complicate treatment. Due to tumor heterogeneity, current limited research shows that PD-1 or PD-L1 monoclonal antibody drug resistance may be related to the following factors: mutation of tumor antigen and antigen presentation process, multiple immune checkpoint interactions, immune microenvironment changes dynamically, activation of oncogenic pathways, gene mutation and epigenetic changes of key proteins in tumors, tumor competitive metabolism, and accumulation of metabolites, etc, mechanisms of resistance are complex. Therefore, it is the most urgent task to further elucidate the mechanism of immune checkpoint inhibitor resistance, discover multitumor universal

biomarkers, and develop new target agents to improve the response rate of immunotherapy in patients (206). It has been shown that there is also a strong link between circRNAs and ICIs treatment resistance. Zhang et al. found circFGFR1 could directly interact with miR-381-3p and subsequently act as a miRNA sponge to upregulate the expression of the miR-381-3p target gene C-X-C motif chemokine receptor 4 (CXCR4), which promoted NSCLC progression and resistance to anti-programmed cell death 1 (PD-1)-based therapy in non-small cell lung cancer cells (24). Interestingly, Hong et al. found that knock-down of circ-CPA4 inhibited intracellular and extracellular PD-L1 by targeting let-7 miRNA. On the one hand, PD-L1 self-regulated NSCLC cell growth, mobility, stemness and chemoresistance to cisplatin treatment. On the other, secreted PD-L1 inactivated CD8 T cells by activating extracellular and intracellular pathways mediated cell death to facilitate immune evasion (25). There are many more reports on circRNAs regulating resistance to ICIs, mainly against PD-1 and PD-L1 in breast cancer and hepatocellular carcinoma (65, 134). CircRNAs regarding anti-CTLA-4 resistance are rare by comparison, but there are reports of circRNAs targeting CTLA4 *via* ceRNA (competing endogenous RNAs) mechanisms to regulate tumor tumorigenesis (207, 208). Since ICIs treatment is closely related to T cell immunity and tumor microenvironment, and circRNA also plays an important role in this regard, I think the possible relationship of circRNA in future ICIs treatment cannot be ignored.

## CONCLUSION AND PERSPECTIVE

Tumor resistance is now known to be facilitated by factors affecting increased drug efflux transporters or reduced influx channels, enhanced EMT and stem cellularity, alterations in target gene copy number and the activation of bypass pathways or downstream signaling, endoplasmic reticulum stress, the remodeling of autophagy and phagocytosis, enhanced or

diminished DNA repair capacity, and alterations in the TME (Figure 6). This paper summarizes the links between the above mechanisms and circRNAs. From the beginning, circRNA was considered to be the “junk” in the cell, Research in recent years has discovered functions of circRNAs ranging from being microRNA (miRNA) sponges and transcription regulators to having protein in teractions and allowing for translation. The function and mechanism of action of circRNAs in tumors is becoming increasingly complex, especially after considering again the function of circ’s encoded proteins, the binding of a previously large number of circRNAs to downstream targets does not seem to be so pure. This also predetermines the diversity of circRNAs functions, in this case, the integration of the same circRNAs function is particularly important. In addition to the functional complexity, the function of the same circRNAs in different tumors or different environments is still worth thinking about whether the function of circRNAs will change with the cellular environment. Secondly, regarding the characterization of circRNAs distribution in cells, researchers habitually take the site where circRNAs accumulates more (nucleus or cytoplasm) as the site where circRNAs exerts its function, and whether this is reasonable deserves further consideration. Because, we know that the content of circRNAs varies greatly in different tumors, the circRNAs enriched in a certain type of tumor, even if it is relatively less distributed, may still be quite higher after quantification than in other cells where it is more distributed. The role of circRNAs in tumor cells is also becoming increasingly important, and there exists a great potential to become a molecular marker and therapeutic target for tumors in the future. It is believed that, based on the complex mechanism of drug resistance, it is of no clinical significance to simply search for and regulate drug resistance targets, and it may even produce drug resistance again soon. It is speculated that according to the possible tumor characteristics, three types of treatment methods should be combined to change the tumor microenvironment ecology and eliminate various heterogeneous tumor subsets, so



**FIGURE 6** | Overview of functional circRNAs in various types of cancer. The map shows the circRNAs that have been confirmed to function in various types of cancer. As the mechanism of drug resistance is complex, only the main mechanism is listed in this map. Among the number other mechanisms, specific mechanisms such as the regulation of metabolism, cell cycle, apoptosis, RNA binding proteins (RBPs), immune escape, etc., summed up as alterations in target gene copy number and the activation of bypass pathways or downstream signaling.

as to reduce tumor drug resistance and improve long-term clinical efficacy. Finally, standardizing the nomenclature of circRNAs in publications is imminent. The traditional way of naming circRNAs based on the parent gene has many drawbacks, because it is impossible to distinguish different circRNAs composed of different exons under the same parent gene, and even in many circRNAs related to tumor drug resistance articles do not provide the sequence or location of circRNAs, and the simple parent gene naming makes it impossible for me to target the exact circRNA. Of course, this problem is inevitable, because database inclusion and naming always follows the publication of the researcher's results. I suggest that the first discovered circRNA can follow the nomenclature of the publisher, but subsequent articles need to specify the sequence and composition of the circRNA to distinguish if it is the same circRNA.

## REFERENCES

- Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are Single-Stranded Covalently Closed Circular RNA Molecules Existing as Highly Base-Paired Rod-Like Structures. *Proc Natl Acad Sci USA* (1976) 73 (11):3852–6. doi: 10.1073/pnas.73.11.3852
- Arnberg AC, Van Ommen GJ, Grivell LA, Van Bruggen EF, Borst P. Some Yeast Mitochondrial RNAs Are Circular. *Cell* (1980) 19(2):313–9. doi: 10.1016/0092-8674(80)90505-X
- Chen LL, Yang L. Regulation of circRNA Biogenesis. *RNA Biol* (2015) 12 (4):381–8. doi: 10.1080/15476286.2015.1020271
- Cui C, Yang J, Li X, Liu D, Fu L, Wang X, et al. Functions and Mechanisms of Circular RNAs in Cancer Radiotherapy and Chemotherapy Resistance. *Mol Cancer* (2020) 19(1):58. doi: 10.1186/s12943-020-01180-y
- Xu T, Wang M, Jiang L, Ma L, Wan L, Chen Q, et al. CircRNAs in Anticancer Drug Resistance: Recent Advances and Future Potential. *Mol Cancer* (2020) 19(1):127. doi: 10.1186/s12943-020-01240-3
- Gong J, Luk F, Jaiswal R, George AM, Grau GE, Bebawy M, et al. Circular RNA CRIM1 Functions as a ceRNA to Promote Nasopharyngeal Carcinoma Metastasis and Docetaxel Chemoresistance Through Upregulating FOXQ1. *Mol Cancer* (2020) 19(1):33. doi: 10.1186/s12943-020-01149-x
- Joyce H, McCann A, Clynes M, Larkin A. CircNRIPI Modulates the miR-515-5p/IL-25 Axis to Control 5-Fu and Cisplatin Resistance in Nasopharyngeal Carcinoma. *Drug Design Dev Ther* (2021) 15:323–30. doi: 10.2147/DDDT.S292180
- Planells-Cases R, Lutter D, Guyader C, Gerhards NM, Ullrich F, Elger DA, et al. Exosome-Delivered circRNA Promotes Glycolysis to Induce Chemoresistance Through the miR-122-PKM2 Axis in Colorectal Cancer. *Mol Oncol* (2020) 14(3):539–55. doi: 10.1002/1878-0261.12629
- Saxena M, Stephens MA, Pathak H, Rangarajan A. Exosomal Transfer of Circular RNA FBXW7 Ameliorates the Chemoresistance to Oxaliplatin in Colorectal Cancer by Sponging miR-18b-5p. *Neoplasia* (2021) 68(1):108–18. doi: 10.4149/neo\_2020\_200417N414
- Hua L, Huang L, Zhang X, Feng H, Shen B. Circ-PRKDC Contributes to 5-Fluorouracil Resistance of Colorectal Cancer Cells by Regulating miR-375/FOXMI Axis and Wnt/ $\beta$ -Catenin Pathway. *Onco Targets Ther* (2020) 13:5939–53. doi: 10.2147/OTT.S253468
- Song Y, Hu N, Song X, Yang J. Hsa\_circ\_001680 Affects the Proliferation and Migration of CRC and Mediates its Chemoresistance by Regulating BMI1 Through miR-340. *Mol Cancer* (2020) 19(1):20. doi: 10.1186/s12943-020-1134-8
- Yi X, Chen W, Li C, Chen X, Lin Q, Lin S, et al. Down-Regulation of Circ\_0032833 Sensitizes Colorectal Cancer to 5-Fluorouracil and Oxaliplatin Partly Depending on the Regulation of miR-125-5p and MSI1. *Cancer Manag Res* (2020) 12:11257–69. doi: 10.2147/CMAR.S270123
- Zhang W, Wang Z, Cai G, Huang P. Downregulation of Circ\_0071589 Suppresses Cisplatin Resistance in Colorectal Cancer by Regulating the MiR-526b-3p/KLF12 Axis. *Cancer Manag Res* (2021) 13:2717–31. doi: 10.2147/CMAR.S294880
- Xi L, Liu Q, Zhang W, Luo L, Song J, Liu R, et al. Circular RNA Circscpp1 Knockdown Attenuates Doxorubicin Resistance and Suppresses Tumor Progression of Colorectal Cancer via miR-944/FZD7 Axis. *Cancer Cell Int* (2021) 21(1):153. doi: 10.1186/s12935-021-01855-6
- Ren TJ, Liu C, Hou JF, Shan FX. CircDDX17 Reduces 5-Fluorouracil Resistance and Hinders Tumorigenesis in Colorectal Cancer by Regulating miR-31-5p/KANK1 Axis. *Eur Rev Med Pharmacol Sci* (2020) 24(4):1743–54. doi: 10.26355/eurrev\_202002\_20351
- He X, Ma J, Zhang M, Cui J, Yang H. Circ\_0007031 Enhances Tumor Progression and Promotes 5-Fluorouracil Resistance in Colorectal Cancer Through Regulating miR-133b/ABCC5 Axis. *Cancer Biomark* (2020) 29 (4):531–42. doi: 10.3233/CBM-200023
- Zhao K, Cheng X, Ye Z, Li Y, Peng W, Wu Y, et al. Exosome-Mediated Transfer of Circ\_0000338 Enhances 5-Fluorouracil Resistance in Colorectal Cancer Through Regulating MicroRNA 217 (miR-217) and miR-485-3p. *Mol Cell Biol* (2021) 41(5):e00517–20. doi: 10.1128/MCB.00517-20
- Sun Y, Cao Z, Shan J, Gao Y, Liu X, Ma D, et al. Hsa\_circ\_0020095 Promotes Oncogenesis and Cisplatin Resistance in Colon Cancer by Sponging miR-487a-3p and Modulating Sox9. *Front Cell Dev Biol* (2020) 8:604869. doi: 10.3389/fcell.2020.604869
- Song Y, Hu N, Song X, Yang J. Hsa\_Circ\_0007841 Enhances Multiple Myeloma Chemotherapy Resistance Through Upregulating Abcg2. *Technol Cancer Res Treat* (2020) 19:1533033820928371. doi: 10.1177/1533033820928371
- Liu J, Du F, Chen C, Li D, Chen Y, Xiao X, et al. CircRNA ITCH Increases Bortezomib Sensitivity Through Regulating the miR-615-3p/PRKCD Axis in Multiple Myeloma. *Life Sci* (2020) 262:118506. doi: 10.1016/j.lfs.2020.118506
- Wang Y, Lin Q, Song C, Ma R, Li X. Depletion of Circ\_0007841 Inhibits Multiple Myeloma Development and BTZ Resistance via miR-129-5p/JAG1 Axis. *Cell Cycle* (2020) 19(23):3289–302. doi: 10.1080/15384101.2020.1839701
- Ye Y, Zhao L, Li Q, Xi C, Li Y, Li Z, et al. Circ\_0007385 Served as Competing Endogenous RNA for miR-519d-3p to Suppress Malignant Behaviors and Cisplatin Resistance of Non-Small Cell Lung Cancer Cells. *Thorac Cancer* (2020) 11(8):2196–208. doi: 10.1111/1759-7714.13527
- Zhu X, Han J, Lan H, Lin Q, Wang Y, Sun X. A Novel Circular RNA Hsa\_circRNA\_103809/miR-377-3p/GOT1 Pathway Regulates Cisplatin-Resistance in Non-Small Cell Lung Cancer (NSCLC). *BMC Cancer* (2020) 20(1):1190. doi: 10.1186/s12885-020-07680-w
- Zhang PF, Pei X, Li KS, Jin LN, Wang F, Wu J, et al. Circular RNA Circfgfr1 Promotes Progression and Anti-PD-1 Resistance by Sponging miR-381-3p in Non-Small Cell Lung Cancer Cells. *Mol Cancer* (2019) 18(1):179. doi: 10.1186/s12943-019-1111-2

25. Hong W, Xue M, Jiang J, Zhang Y, Gao X. Circular RNA Circ-CPA4/ Let-7 miRNA/PD-L1 Axis Regulates Cell Growth, Stemness, Drug Resistance and Immune Evasion in Non-Small Cell Lung Cancer (NSCLC). *J Exp Clin Cancer Res* (2020) 39(1):149. doi: 10.1186/s13046-020-01648-1
26. Pang J, Ye L, Zhao D, Zhao D, Chen Q, et al. Circular RNA PRMT5 Confers Cisplatin-Resistance via miR-4458/REV3L Axis in Non-Small-Cell Lung Cancer. *Cell Biol Int* (2020) 44(12):2416–26. doi: 10.1002/cbin.11449
27. Lu H, Xie X, Wang K, Chen Q, Cai S, Liu D, et al. Circular RNA Hsa\_Circ\_0096157 Contributes to Cisplatin Resistance by Proliferation, Cell Cycle Progression, and Suppressing Apoptosis of Non-Small-Cell Lung Carcinoma Cells. *Mol Cell Biochem* (2020) 475(1-2):63–77. doi: 10.1007/s11010-020-03860-1
28. Zhou Y, Zheng X, Xu B, Chen L, Wang Q, Deng H, et al. Circular RNA Hsa\_Circ\_0004015 Regulates the Proliferation, Invasion, and TKI Drug Resistance of Non-Small Cell Lung Cancer by miR-1183/PDPK1 Signaling Pathway. *Biochem Biophys Res Commun* (2019) 508(2):527–35. doi: 10.1016/j.bbrc.2018.11.157
29. Kong R. Circular RNA Hsa\_Circ\_0085131 is Involved in Cisplatin-Resistance of Non-Small-Cell Lung Cancer Cells by Regulating Autophagy. *Cell Biol Int* (2020) 44(9):1945–56. doi: 10.1002/cbin.11401
30. Chen C, Zhang M, Zhang Y. Circ\_0000079 Deceals the RNA-Binding Protein FXR1 to Interrupt Formation of the FXR1/PRCKI Complex and Decline Their Mediated Cell Invasion and Drug Resistance in NSCLC. *Cell Transplant* (2020) 29:963689720961070. doi: 10.1177/0963689720961070
31. Dong Y, Xu T, Zhong S, Wang B, Zhang H, Wang X, et al. Circ\_0076305 Regulates Cisplatin Resistance of Non-Small Cell Lung Cancer via Positively Modulating STAT3 by Sponging miR-296-5p. *Life Sci* (2019) 239:116984. doi: 10.1016/j.lfs.2019.116984
32. Li X, Yang B, Ren H, Xiao T, Zhang L, Li L, et al. Hsa\_circ\_0002483 Inhibited the Progression and Enhanced the Taxol Sensitivity of Non-Small Cell Lung Cancer by Targeting miR-182-5p. *Cell Death Dis* (2019) 10(12):953. doi: 10.1038/s41419-019-2180-2
33. Ma J, Qi G, Li L. A Novel Serum Exosomes-Based Biomarker Hsa\_Circ\_0002130 Facilitates Osimertinib-Resistance in Non-Small Cell Lung Cancer by Sponging miR-498. *Onco Targets Ther* (2020) 13:5293–307. doi: 10.2147/OTT.S243214
34. Guo C, Wang H, Jiang H, Qiao L, Wang X. Circ\_0011292 Enhances Paclitaxel Resistance in Non-Small Cell Lung Cancer by Regulating miR-379-5p/TRIM65 Axis. *Cancer Biother Radiopharm* (2020) 37(2):84–95. doi: 10.1089/cbr.2019.3546
35. Xu X, Tao R, Sun L, Ji X. Exosome-Transferred Hsa\_Circ\_0014235 Promotes DDP Chemoresistance and Deteriorates the Development of Non-Small Cell Lung Cancer by Mediating the miR-520a-5p/CDK4 Pathway. *Cancer Cell Int* (2020) 20(1):552. doi: 10.1186/s12935-020-01642-9
36. Li YH, Xu CL, He CJ, Pu HH, Liu JL, Wang Y, et al. circMTDH.4/miR-630/AEG-1 Axis Participates in the Regulation of Proliferation, Migration, Invasion, Chemoresistance, and Radioresistance of NSCLC. *Mol Carcinog* (2020) 59(2):141–53. doi: 10.1002/mc.23135
37. Yang B, Teng F, Chang L, Wang J, Liu DL, Cui YS, et al. Tumor-Derived Exosomal circRNA\_102481 Contributes to EGFR-TKIs Resistance via the miR-30a-5p/ROR1 Axis in Non-Small Cell Lung Cancer. *Aging (Albany NY)* (2021) 13(9):13264–86. doi: 10.18632/aging.203011
38. Geng J, Yang K. Circ\_0011292 Regulates Oxidative Stress and FGF9 to Enhance Chemoresistance of Non-Small Cell Lung Cancer via Sponging miR-187-3p. *DNA Cell Biol* (2021) 40(5):675–82. doi: 10.1089/dna.2020.6412
39. Zhang W, Song C, Ren X. Circ\_0003998 Regulates the Progression and Docetaxel Sensitivity of DTX-Resistant Non-Small Cell Lung Cancer Cells by the miR-136-5p/CORO1C Axis. *Technol Cancer Res Treat* (2021) 20:1533033821990040. doi: 10.1177/1533033821990040
40. Shi Q, Ji T, Ma Z, Tan Q, Liang J. Serum Exosomes-Based Biomarker Circ\_0008928 Regulates Cisplatin Sensitivity, Tumor Progression, and Glycolysis Metabolism by miR-488/HK2 Axis in Cisplatin-Resistant Nonsmall Cell Lung Carcinoma. *Cancer Biother Radiopharm* (2021). doi: 10.1089/cbr.2020.4490
41. Song HM, Meng D, Wang JP, Zhang XY. circRNA Hsa\_Circ\_0005909 Predicts Poor Prognosis and Promotes the Growth, Metastasis, and Drug Resistance of Non-Small-Cell Lung Cancer via the miRNA-338-3p/SOX4 Pathway. *Dis Markers* (2021) 2021:8388512. doi: 10.1155/2021/8388512
42. Liang H, Lin Z, Lin H, Zhao L, Huang W. circRNA\_103615 Contributes to Tumor Progression and Cisplatin Resistance in NSCLC by Regulating ABCB1. *Exp Ther Med* (2021) 22(3):934. doi: 10.3892/etm.2021.10366
43. Li J, Fan R, Xiao H. Circ\_ZFR Contributes to the Paclitaxel Resistance and Progression of Non-Small Cell Lung Cancer by Upregulating KPNA4 Through Sponging miR-195-5p. *Cancer Cell Int* (2021) 21(1):15. doi: 10.1186/s12935-020-01702-0
44. Feng N, Guo Z, Wu X, Tian Y, Li Y, Geng Y, et al. Circ\_PIP5K1A Regulates Cisplatin Resistance and Malignant Progression in Non-Small Cell Lung Cancer Cells and Xenograft Murine Model via Depending on miR-493-5p/ROCK1 Axis. *Respir Res* (2021) 22(1):248. doi: 10.1186/s12931-021-01840-7
45. Yu L, Li J, Peng B, Cai P, Zhao B, Chen Y, et al. CircASXL1 Knockdown Restrains Hypoxia-Induced DDP Resistance and NSCLC Progression by Sponging miR-206. *Cancer Manag Res* (2021) 13:5077–89. doi: 10.2147/CMAR.S276964
46. Zhang Y, Ge P, Zhou D, Xing R, Bai L. Circular RNA FOXO3 Accelerates Glycolysis and Improves Cisplatin Sensitivity in Lung Cancer Cells via the miR-543/Foxo3 Axis. *Oncol Lett* (2021) 22(6):839. doi: 10.3892/ol.2021.13100
47. Li C, Zhang J, Yang X, Hu C, Chu T, Zhong R, et al. Hsa\_Circ\_0003222 Accelerates Stemness and Progression of Non-Small Cell Lung Cancer by Sponging miR-527. *Cell Death Dis* (2021) 12(9):807. doi: 10.1038/s41419-021-04095-8
48. Xu J, Ni L, Zhao F, Dai X, Tao J, Pan J, et al. Overexpression of Hsa\_Circ\_0002874 Promotes Resistance of Non-Small Cell Lung Cancer to Paclitaxel by Modulating miR-1273f/MDM2/p53 Pathway. *Aging (Albany NY)* (2021) 13(4):5986–6009. doi: 10.18632/aging.202521
49. Yu X, Fu X, Zhang X, Bai C, Wang Y. Circ\_0001658 Regulates Gefitinib Resistance of Non-Small Cell Lung Cancer Through miR-409-3p/TWIST1 Axis. *Anticancer Drugs* (2021) 33(2):158–66. doi: 10.1097/CAD.0000000000001257
50. Xu Y, Zhao R, Wang H, Jiang J, Wang Z, Wang J, et al. Circular RNA PRMT5 Knockdown Enhances Cisplatin Sensitivity and Immune Response in Non-Small Cell Lung Cancer by Regulating miR-138-5p/MYH9 Axis. *J buon* (2021) 26(5):1850–61.
51. Wang X, Wang H, Jiang H, Qiao L, Guo C. Circular RNA circ\_0076305 Promotes Cisplatin (DDP) Resistance of Non-Small Cell Lung Cancer Cells by Regulating ABCC1 Through miR-186-5p. *Cancer Biother Radiopharm* (2021). doi: 10.1089/cbr.2020.4153
52. Shao N, Song L, Sun X. Exosomal Circ\_PIP5K1A Regulates the Progression of Non-Small Cell Lung Cancer and Cisplatin Sensitivity by miR-101/ABCC1 Axis. *Mol Cell Biochem* (2021) 476(6):2253–67. doi: 10.1007/s11010-021-04083-8
53. Chen SW, Zhu SQ, Pei X, Qiu BQ, Xiong D, Long X, et al. Cancer Cell-Derived Exosomal Circusp7 Induces CD8(+) T Cell Dysfunction and Anti-PD1 Resistance by Regulating the miR-934/SHP2 Axis in NSCLC. *Mol Cancer* (2021) 20(1):144. doi: 10.1186/s12943-021-01448-x
54. Du D, Cao X, Duan X, Zhang X. Blocking Circ\_0014130 Suppressed Drug Resistance and Malignant Behaviors of Docetaxel Resistance-Acquired NSCLC Cells via Regulating miR-545-3p-YAP1 Axis. *Cytotechnology* (2021) 73(4):571–84. doi: 10.1007/s10616-021-00478-z
55. Liu Y, Zhai R, Hu S, Liu J. Circular RNA Circ-RNF121 Contributes to Cisplatin (DDP) Resistance of Non-Small-Cell Lung Cancer Cells by Regulating the miR-646/SOX4 Axis. *Anticancer Drugs* (2022) 33(1):e186–97. doi: 10.1097/CAD.0000000000001184
56. Liu Y, Li C, Liu H, Wang J. Circ\_0001821 Knockdown Suppresses Growth, Metastasis, and TAX Resistance of Non-Small-Cell Lung Cancer Cells by Regulating the miR-526b-5p/GRK5 Axis. *Pharmacol Res Perspect* (2021) 9(4):e00812. doi: 10.1002/prp2.812
57. Zhu K, Zhu J, Geng J, Zhang Y, Qin Y, Wang F, et al. Circsnx6 (Hsa\_Circ\_0031608) Enhances Drug Resistance of Non-Small Cell Lung Cancer (NSCLC) via miR-137. *Biochem Biophys Res Commun* (2021) 567:79–85. doi: 10.1016/j.bbrc.2021.06.032
58. Liu Z, Wang T, She Y, Wu K, Gu S, Li L, et al. N(6)-Methyladenosine-Modified Circigf2bp3 Inhibits CD8(+) T-Cell Responses to Facilitate Tumor Immune Evasion by Promoting the Deubiquitination of PD-L1 in Non-

- Small Cell Lung Cancer. *Mol Cancer* (2021) 20(1):105. doi: 10.1186/s12943-021-01398-4
59. Zhong Y, Lin H, Li Q, Liu C, Shen J. CircRNA\_100565 Contributes to Cisplatin Resistance of NSCLC Cells by Regulating Proliferation, Apoptosis and Autophagy via miR-337-3p/ADAM28 Axis. *Cancer Biomark* (2021) 30(2):261–73. doi: 10.3233/CBM-201705
  60. Xu Y, Jiang T, Wu C, Zhang Y. CircAKT3 Inhibits Glycolysis Balance in Lung Cancer Cells by Regulating miR-516b-5p/STAT3 to Inhibit Cisplatin Sensitivity. *Biotechnol Lett* (2020) 42(7):1123–35. doi: 10.1007/s10529-020-02846-9
  61. Li X, Feng Y, Yang B, Xiao T, Ren H, Yu X, et al. A Novel Circular RNA, Hsa\_Circ\_0030998 Suppresses Lung Cancer Tumorigenesis and Taxol Resistance by Sponging miR-558. *Mol Oncol* (2021) 15(8):2235–48. doi: 10.1002/1878-0261.12852
  62. Wu Z, Gong Q, Yu Y, Zhu J, Li W. Knockdown of Circ-ABCB10 Promotes Sensitivity of Lung Cancer Cells to Cisplatin via miR-556-3p/AK4 Axis. *BMC Pulm Med* (2020) 20(1):10. doi: 10.1186/s12890-019-1035-z
  63. Zheng F, Xu R. CircPVT1 Contributes to Chemotherapy Resistance of Lung Adenocarcinoma Through miR-145-5p/ABCC1 Axis. *BioMed Pharmacother* (2020) 124:109828. doi: 10.1016/j.biopha.2020.109828
  64. Wang T, Liu Z, She Y, Deng J, Zhong Y, Zhao M, et al. A Novel Protein Encoded by Circask1 Ameliorates Gefitinib Resistance in Lung Adenocarcinoma by Competitively Activating ASK1-Dependent Apoptosis. *Cancer Lett* (2021) 520:321–31. doi: 10.1016/j.canlet.2021.08.007
  65. Huang XY, Zhang PF, Wei CY, Peng R, Lu JC, Gao C, et al. Circular RNA circMET Drives Immunosuppression and Anti-PD1 Therapy Resistance in Hepatocellular Carcinoma via the miR-30-5p/Snai1/DPP4 Axis. *Mol Cancer* (2020) 19(1):92. doi: 10.1186/s12943-020-01213-6
  66. Zhang PF, Gao C, Huang XY, Lu JC, Guo XJ, Shi GM, et al. Cancer Cell-Derived Exosomal Circuhrf1 Induces Natural Killer Cell Exhaustion and may Cause Resistance to Anti-PD1 Therapy in Hepatocellular Carcinoma. *Mol Cancer* (2020) 19(1):110. doi: 10.1186/s12943-020-01222-5
  67. Xu J, Wan Z, Tang M, Lin Z, Jiang S, Ji L, et al. N(6)-Methyladenosine-Modified CircRNA-SORE Sustains Sorafenib Resistance in Hepatocellular Carcinoma by Regulating  $\beta$ -Catenin Signaling. *Mol Cancer* (2020) 19(1):163. doi: 10.1186/s12943-020-01281-8
  68. Li J, Qin X, Wu R, Wan L, Zhang L, Liu R, et al. Circular RNA Circfbxo11 Modulates Hepatocellular Carcinoma Progress and Oxaliplatin Resistance Through miR-605/FOXO3/ABCB1 Axis. *J Cell Mol Med* (2020) 24(9):5152–61. doi: 10.1111/jcmm.15162
  69. Xu J, Ji L, Liang Y, Wan Z, Zheng W, Song X, et al. CircRNA-SORE Mediates Sorafenib Resistance in Hepatocellular Carcinoma by Stabilizing YBX1. *Signal Transduct Target Ther* (2020) 5(1):298. doi: 10.1038/s41392-020-00375-5
  70. Li Y, Zhang Y, Zhang S, Huang D, Li B, Liang G, et al. circRNA Circarnt2 Suppressed the Sensitivity of Hepatocellular Carcinoma Cells to Cisplatin by Targeting the miR-155-5p/PDK1 Axis. *Mol Ther Nucleic Acids* (2021) 23:244–54. doi: 10.1016/j.omtn.2020.08.037
  71. Fan W, Chen L, Wu X, Zhang T. Circ\_0031242 Silencing Mitigates the Progression and Drug Resistance in DDP-Resistant Hepatoma Cells by the miR-924/POU3F2 Axis. *Cancer Manag Res* (2021) 13:743–55. doi: 10.2147/CMAR.S272851
  72. Qin L, Zhan Z, Wei C, Li X, Zhang T, Li J. Hsa-circRNA-G004213 Promotes Cisplatin Sensitivity by Regulating Mir-513b-5p/PRPF39 in Liver Cancer. *Mol Med Rep* (2021) 23(6):421. doi: 10.3892/mmr.2021.12060
  73. Weng H, Zeng L, Cao L, Chen T, Li Y, Xu Y, et al. Circfoxm1 Contributes to Sorafenib Resistance of Hepatocellular Carcinoma Cells by Regulating MECP2 via miR-1324. *Mol Ther Nucleic Acids* (2021) 23:811–20. doi: 10.1016/j.omtn.2020.12.019
  74. Huang W, Huang F, Feng C. CircFoxo3 Promotes Adriamycin Resistance Through Regulation of miR-199a-5p/ATP Binding Cassette Subfamily C Member 1 Axis in Hepatocellular Carcinoma. *Onco Targets Ther* (2020) 13:5113–22. doi: 10.2147/OTT.S243571
  75. Li X, He J, Ren X, Zhao H, Zhao H. Circ\_0003998 Enhances Doxorubicin Resistance in Hepatocellular Carcinoma by Regulating miR-218-5p/EIF5A2 Pathway. *Diagn Pathol* (2020) 15(1):141. doi: 10.1186/s13000-020-01056-1
  76. Li P, Song R, Yin F, Liu M, Liu H, Ma S, et al. Circmrps35 Promotes Malignant Progression and Cisplatin Resistance in Hepatocellular Carcinoma. *Mol Ther* (2022) 30(1):431–47. doi: 10.1016/j.yth.2021.08.02
  77. Chen M, Ai G, Zhou J, Mao W, Li H, Guo J, et al. Circmt01 Promotes Tumorigenesis and Chemoresistance of Cervical Cancer via Regulating miR-6893. *BioMed Pharmacother* (2019) 117:109064. doi: 10.1016/j.biopha.2019.109064
  78. Guo J, Chen M, Ai G, Mao W, Li H, Zhou J, et al. Hsa\_circ\_0023404 Enhances Cervical Cancer Metastasis and Chemoresistance Through VEGFA and Autophagy Signaling by Sponging miR-5047. *BioMed Pharmacother* (2019) 115:108957. doi: 10.1016/j.biopha.2019.108957
  79. Li X, Liu Y, Zhang X, Shen J, Xu R, Liu Y, et al. Circular RNA Hsa\_Circ\_0000073 Contributes to Osteosarcoma Cell Proliferation, Migration, Invasion and Methotrexate Resistance by Sponging miR-145-5p and miR-151-3p and Upregulating NRAS. *Aging (Albany NY)* (2020) 12(14):14157–73. doi: 10.18632/aging.103423
  80. Kun-Peng Z, Xiao-Long M, Chun-Lin Z. Overexpressed Circpvt1, a Potential New Circular RNA Biomarker, Contributes to Doxorubicin and Cisplatin Resistance of Osteosarcoma Cells by Regulating ABCB1. *Int J Biol Sci* (2018) 14(3):321–30. doi: 10.7150/ijbs.24360
  81. Gong X, Li W, Dong L, Qu F. CircUBAP2 Promotes SEMA6D Expression to Enhance the Cisplatin Resistance in Osteosarcoma Through Sponging miR-506-3p by Activating Wnt/ $\beta$ -Catenin Signaling Pathway. *J Mol Histol* (2020) 51(4):329–40. doi: 10.1007/s10735-020-09883-8
  82. Zhou W, Liu Y, Wu X. Down-Regulation of circITCH Promotes Osteosarcoma Development and Resistance to Doxorubicin via the miR-524/RASSF6 Axis. *J Gene Med* (2021) 23(10):e3373. doi: 10.1002/jgm.3373
  83. Wei W, Ji L, Duan W, Zhu J. Circular RNA Circ\_0081001 Knockdown Enhances Methotrexate Sensitivity in Osteosarcoma Cells by Regulating miR-494-3p/TGM2 Axis. *J Orthop Surg Res* (2021) 16(1):50. doi: 10.1186/s13018-020-02169-5
  84. Yuan J, Liu Y, Zhang Q, Ren Z, Li G, Tian R, et al. CircPRDM2 Contributes to Doxorubicin Resistance of Osteosarcoma by Elevating EZH2 via Sponging miR-760. *Cancer Manag Res* (2021) 13:4433–45. doi: 10.2147/CMAR.S295147
  85. Wei CY, Zhu MX, Lu NH, Liu JQ, Yang YW, Zhang Y, et al. Circular RNA Circ\_0020710 Drives Tumor Progression and Immune Evasion by Regulating the miR-370-3p/CXCL12 Axis in Melanoma. *Mol Cancer* (2020) 19(1):84. doi: 10.1186/s12943-020-01191-9
  86. Yi X, Chen W, Li C, Chen X, Lin Q, Lin S, et al. Circular RNA Circ\_0004507 Contributes to Laryngeal Cancer Progression and Cisplatin Resistance by Sponging miR-873 to Upregulate Multidrug Resistance 1 and Multidrug Resistance Protein 1. *Head Neck* (2021) 43(3):928–41. doi: 10.1002/hed.26549
  87. Feng B, Chen K, Zhang W, Zheng Q, He Y. Circpgam1 Enhances Autophagy Signaling During Laryngocarcinoma Drug Resistance by Regulating miR-376a. *Biochem Biophys Res Commun* (2021) 534:966–72. doi: 10.1016/j.bbrc.2020.10.063
  88. Shang J, Chen WM, Liu S, Wang ZH, Wei TN, Chen ZZ, et al. CircPAN3 Contributes to Drug Resistance in Acute Myeloid Leukemia Through Regulation of Autophagy. *Leuk Res* (2019) 85:106198. doi: 10.1016/j.leukres.2019.106198
  89. Shang J, Chen WM, Wang ZH, Wei TN, Chen ZZ, Wu WB, et al. CircPAN3 Mediates Drug Resistance in Acute Myeloid Leukemia Through the miR-153-5p/miR-183-5p-XIAP Axis. *Exp Hematol* (2019) 70:42–54.e3. doi: 10.1016/j.exphem.2018.10.011
  90. Liu F, Zhang J, Qin L, Yang Z, Xiong J, Zhang Y, et al. Circular RNA EIF6 (Hsa\_circ\_0060060) Sponges miR-144-3p to Promote the Cisplatin-Resistance of Human Thyroid Carcinoma Cells by Autophagy Regulation. *Aging (Albany NY)* (2018) 10(12):3806–20. doi: 10.18632/aging.101674
  91. Hua L, Huang L, Zhang X, Feng H, Shen B. Knockdown of Circular RNA CEP128 Suppresses Proliferation and Improves Cytotoxic Efficacy of Temozolomide in Glioma Cells by Regulating miR-145-5p. *Neuroreport* (2019) 30(18):1231–8. doi: 10.1097/WNR.0000000000001326
  92. Ding C, Yi X, Wu X, Bu X, Wang D, Wu Z, et al. Exosome-Mediated Transfer of circRNA CircNFIX Enhances Temozolomide Resistance in Glioma. *Cancer Lett* (2020) 479:1–12. doi: 10.1016/j.canlet.2020.03.002

93. Han C, Wang S, Wang H, Zhang J. Exosomal circ-HIPK3 Facilitates Tumor Progression and Temozolomide Resistance by Regulating miR-421/ZIC5 Axis in Glioma. *Cancer Biother Radiopharm* (2021) 36(7):537–48. doi: 10.1089/cbr.2019.3492
94. Yin H, Cui X. Knockdown of Circhipk3 Facilitates Temozolomide Sensitivity in Glioma by Regulating Cellular Behaviors Through miR-524-5p/KIF2A-Mediated PI3K/AKT Pathway. *Cancer Biother Radiopharm* (2021) 36(7):556–67. doi: 10.1089/cbr.2020.3575
95. Ding C, Yi X, Chen X, Wu Z, You H, Chen X, et al. Warburg Effect-Promoted Exosomal Circ\_0072083 Releasing Up-Regulates NANGO Expression Through Multiple Pathways and Enhances Temozolomide Resistance in Glioma. *J Exp Clin Cancer Res* (2021) 40(1):164. doi: 10.1186/s13046-021-01942-6
96. Wei Y, Lu C, Zhou P, Zhao L, Lyu X, Yin J, et al. EIF4A3-Induced Circular RNA ASAP1 Promotes Tumorigenesis and Temozolomide Resistance of Glioblastoma via NRAS/MEK1/ERK1-2 Signaling. *Neuro Oncol* (2021) 23(4):611–24. doi: 10.1093/neuonc/noaa214
97. Deng Y, Zhu H, Xiao L, Liu C, Meng X. Circ\_0005198 Enhances Temozolomide Resistance of Glioma Cells Through miR-198/TRIM14 Axis. *Aging (Albany NY)* (2020) 13(2):2198–211. doi: 10.18632/aging.202234
98. Gao F, Han J, Wang Y, Jia L, Luo W, Zeng Y. Circ\_0109291 Promotes the Cisplatin Resistance of Oral Squamous Cell Carcinoma by Sponging miR-188-3p to Increase ABCB1 Expression. *Cancer Biother Radiopharm* (2020). doi: 10.1089/cbr.2020.3928
99. Qiu F, Qiao B, Zhang N, Fang Z, Feng L, Zhang S, et al. Blocking Circ-SCMH1 (Hsa\_Circ\_0011946) Suppresses Acquired DDP Resistance of Oral Squamous Cell Carcinoma (OSCC) Cells Both In Vitro and In Vivo by Sponging miR-338-3p and Regulating LIN28B. *Cancer Cell Int* (2021) 21(1):412. doi: 10.1186/s12935-021-02110-8
100. Zhao Z, Ji M, Wang Q, He N, Li Y. Circular RNA Cdr1as Upregulates SCAI to Suppress Cisplatin Resistance in Ovarian Cancer via miR-1270 Suppression. *Mol Ther Nucleic Acids* (2019) 18:24–33. doi: 10.1016/j.omtn.2019.07.012
101. Xia B, Zhao Z, Wu Y, Wang Y, Zhao Y, Wang J, et al. Circular RNA Circntpo3 Regulates Paclitaxel Resistance of Ovarian Cancer Cells by miR-1299/NEK2 Signaling Pathway. *Mol Ther Nucleic Acids* (2020) 21:780–91. doi: 10.1016/j.omtn.2020.06.002
102. Guo M, Li S, Zhao X, Yuan Y, Zhang B, Guan Y, et al. Knockdown of Circular RNA Hsa\_circ\_0000714 Can Regulate RAB17 by Sponging miR-370-3p to Reduce Paclitaxel Resistance of Ovarian Cancer Through CDK6/RB Pathway. *Oncotargets Ther* (2020) 13:13211–24. doi: 10.2147/OTT.S285153
103. Zhang S, Cheng J, Quan C, Wen H, Feng Z, Hu Q, et al. Circelsr1 (Hsa\_Circ\_0063809) Contributes to Paclitaxel Resistance of Ovarian Cancer Cells by Regulating FOXR2 Expression via miR-1252. *Mol Ther Nucleic Acids* (2020) 19:718–30. doi: 10.1016/j.omtn.2019.12.005
104. Luo Y, Gui R. Circulating Exosomal Circfoxp1 Confers Cisplatin Resistance in Epithelial Ovarian Cancer Cells. *J Gynecol Oncol* (2020) 31(5):e75. doi: 10.3802/jgo.2020.31.e75
105. Li M, Cai J, Han X, Ren Y. Downregulation of Circnrip1 Suppresses the Paclitaxel Resistance of Ovarian Cancer via Regulating the miR-211-5p/HOXC8 Axis. *Cancer Manag Res* (2020) 12:9159–71. doi: 10.2147/CMAR.S268872
106. Cao Y, Xie X, Li M, Gao Y. CircHIPK2 Contributes to DDP Resistance and Malignant Behaviors of DDP-Resistant Ovarian Cancer Cells Both In Vitro and In Vivo Through Circchipk2/miR-338-3p/CHTOP ceRNA Pathway. *Oncotargets Ther* (2021) 14:3151–65. doi: 10.2147/OTT.S291823
107. Wei S, Qi L, Wang L. Overexpression of Circ\_CELSR1 Facilitates Paclitaxel Resistance of Ovarian Cancer by Regulating miR-149-5p/SIK2 Axis. *Anticancer Drugs* (2021) 32(5):496–507. doi: 10.1097/CAD.0000000000001058
108. Che H, Ding H, Jia X. Circ\_0080145 Enhances Imatinib Resistance of Chronic Myeloid Leukemia by Regulating miR-326/PPF1A1 Axis. *Cancer Biother Radiopharm* (2020). doi: 10.1089/cbr.2020.3600
109. Cao HX, Miao CF, Sang LN, Huang YM, Zhang R, Sun L, et al. Circ\_0009910 Promotes Imatinib Resistance Through ULK1-Induced Autophagy by Sponging miR-34a-5p in Chronic Myeloid Leukemia. *Life Sci* (2020) 243:117255. doi: 10.1016/j.lfs.2020.117255
110. Xie F, Zhao N, Zhang H, Xie D. Circular RNA CircHIPK3 Promotes Gemcitabine Sensitivity in Bladder Cancer. *J Cancer* (2020) 11(7):1907–12. doi: 10.7150/jca.39722
111. Huang W, Lu Y, Wang F, Huang X, Yu Z. Circular RNA circRNA\_103809 Accelerates Bladder Cancer Progression and Enhances Chemo-Resistance by Activation of miR-516a-5p/FBXL18 Axis. *Cancer Manag Res* (2020) 12:7561–8. doi: 10.2147/CMAR.S263083
112. Su Y, Yang W, Jiang N, Shi J, Chen L, Zhong G, et al. Hypoxia-Elevated Circelp3 Contributes to Bladder Cancer Progression and Cisplatin Resistance. *Int J Biol Sci* (2019) 15(2):441–52. doi: 10.7150/ijbs.26826
113. Chi BJ, Zhao DM, Liu L, Yin XZ, Wang FF, Bi S, et al. Downregulation of Hsa\_Circ\_0000285 Serves as a Prognostic Biomarker for Bladder Cancer and Is Involved in Cisplatin Resistance. *Neoplasma* (2019) 66(2):197–202. doi: 10.4149/neo\_2018\_180318N185
114. Zhang H, Xiao X, Wei W, Huang C, Wang M, Wang L, et al. CircLIFR Synergizes With MSH2 to Attenuate Chemoresistance via Muts $\alpha$ /ATM-P73 Axis in Bladder Cancer. *Mol Cancer* (2021) 20(1):70. doi: 10.1186/s12943-021-01360-4
115. Wei W, Sun J, Zhang H, Xiao X, Huang C, Wang L, et al. Circ0008399 Interaction With WTAP Promotes Assembly and Activity of the M6a Methyltransferase Complex and Promotes Cisplatin Resistance in Bladder Cancer. *Cancer Res* (2021) 81(24):6142–56. doi: 10.1158/0008-5472.CAN-21-1518
116. Shen Z, Zhou L, Zhang C, Xu J. Reduction of Circular RNA Foxo3 Promotes Prostate Cancer Progression and Chemoresistance to Docetaxel. *Cancer Lett* (2020) 468:88–101. doi: 10.1016/j.canlet.2019.10.006
117. Wu G, Sun Y, Xiang Z, Wang K, Liu B, Xiao G, et al. Preclinical Study Using Circular RNA 17 and Micro RNA 181c-5p to Suppress the Enzalutamide-Resistant Prostate Cancer Progression. *Cell Death Dis* (2019) 10(2):37. doi: 10.1038/s41419-018-1048-1
118. Gao Y, Liu J, Huan J, Che F. Downregulation of Circular RNA Hsa\_Circ\_0000735 Boosts Prostate Cancer Sensitivity to Docetaxel via Sponging miR-7. *Cancer Cell Int* (2020) 20:334. doi: 10.1186/s12935-020-01421-6
119. Li S, Yu C, Zhang Y, Liu J, Jia Y, Sun F, et al. Circular RNA Cir-ITCH Is a Potential Therapeutic Target for the Treatment of Castration-Resistant Prostate Cancer. *BioMed Res Int* (2020) p:7586521. doi: 10.1155/2020/7586521
120. Zhang H, Li M, Zhang J, Shen Y, Gui Q. Exosomal Circ-XIAP Promotes Docetaxel Resistance in Prostate Cancer by Regulating miR-1182/TPD52 Axis. *Drug Des Devel Ther* (2021) 15:1835–49. doi: 10.2147/DDDT.S300376
121. Li H, Li Q, He S. Hsa\_circ\_0025202 Suppresses Cell Tumorigenesis and Tamoxifen Resistance via miR-197-3p/HIPK3 Axis in Breast Cancer. *World J Surg Oncol* (2021) 19(1):39. doi: 10.1186/s12957-021-02149-x
122. Sang Y, Chen B, Song X, Li Y, Liang Y, Han D, et al. circRNA\_0025202 Regulates Tamoxifen Sensitivity and Tumor Progression via Regulating the miR-182-5p/FOXO3a Axis in Breast Cancer. *Mol Ther* (2019) 27(9):1638–52. doi: 10.1016/j.ymthe.2019.05.011
123. Liang Y, Song X, Li Y, Su P, Han D, Ma T, et al. Circckdm4c Suppresses Tumor Progression and Attenuates Doxorubicin Resistance by Regulating miR-548p/PBLD Axis in Breast Cancer. *Oncogene* (2019) 38(42):6850–66. doi: 10.1038/s41388-019-0926-z
124. Liu Y, Dong Y, Zhao L, Su L, Luo J. Circular RNA-MTO1 Suppresses Breast Cancer Cell Viability and Reverses Monastrol Resistance Through Regulating the TRAF4/Eg5 Axis. *Int J Oncol* (2018) 53(4):1752–62. doi: 10.3892/ijo.2018.4485
125. Yang W, Gong P, Yang Y, Yang C, Yang B, Ren L, et al. Circ-ABCB10 Contributes to Paclitaxel Resistance in Breast Cancer Through Let-7a-5p/DUSP7 Axis. *Cancer Manag Res* (2020) 12:2327–37. doi: 10.2147/CMAR.S238513
126. Yang W, Gu J, Wang X, Wang Y, Feng M, Zhou D, et al. Inhibition of Circular RNA CDR1as Increases Chemosensitivity of 5-FU-Resistant BC Cells Through Up-Regulating miR-7. *J Cell Mol Med* (2019) 23(5):3166–77. doi: 10.1111/jcmm.14171

127. Zang H, Li Y, Zhang X, Huang G, et al. Circ-RNF111 Contributes to Paclitaxel Resistance in Breast Cancer by Elevating E2F3 Expression via miR-140-5p. *Thorax Cancer* (2020) 11(7):1891–903. doi: 10.1111/1759-7714.13475
128. Cui Y, Fan J, Shi W, Zhou Z. Circ\_0001667 Knockdown Blocks Cancer Progression and Attenuates Adriamycin Resistance by Depleting NCOA3 via Releasing miR-4458 in Breast Cancer. *Drug Dev Res* (2021) 83(1):75–87. doi: 10.1002/ddr.21845
129. Zhu M, Wang Y, Wang F, Li L, Qiu X. CircFBXL5 Promotes the 5-FU Resistance of Breast Cancer via Modulating miR-216b/HMG2A Axis. *Cancer Cell Int* (2021) 21(1):384. doi: 10.1186/s12935-021-02088-3
130. Yao Y, Li X, Cheng L, Wu X, Wu B. Circular RNA FAT Atypical Cadherin 1 (Circfat1)/microRNA-525-5p/Spindle and Kinetochore-Associated Complex Subunit 1 (SKA1) Axis Regulates Oxaliplatin Resistance in Breast Cancer by Activating the Notch and Wnt Signaling Pathway. *Bioengineered* (2021) 12(1):4032–43. doi: 10.1080/21655979.2021.1951929
131. Hao J, Du X, Lv F, Shi Q. Knockdown of Circ\_0006528 Suppresses Cell Proliferation, Migration, Invasion, and Adriamycin Chemoresistance via Regulating the miR-1236-3p/CHD4 Axis in Breast Cancer. *J Surg Res* (2021) 260:104–15. doi: 10.1016/j.jss.2020.10.031
132. Wu X, Ren Y, Yao R, Zhou L, Fan R. Circular RNA Circ-MMP11 Contributes to Lapatinib Resistance of Breast Cancer Cells by Regulating the miR-153-3p/ANLN Axis. *Front Oncol* (2021) 11:639961. doi: 10.3389/fonc.2021.639961
133. Xie H, Zheng R. Circ\_0085495 Knockdown Reduces Adriamycin Resistance in Breast Cancer Through miR-873-5p/Integrin  $\beta$ 1 Axis. *Anticancer Drugs* (2021) 33(1):e166–77. doi: 10.1097/CAD.0000000000001174
134. Huang L, Ma J, Cui M. Circular RNA Hsa\_Circ\_0001598 Promotes Programmed Death-Ligand-1-Mediated Immune Escape and Trastuzumab Resistance via Sponging miR-1184 in Breast Cancer Cells. *Immunol Res* (2021) 69(6):558–67. doi: 10.1007/s12026-021-09237-w
135. Hu K, Liu X, Li Y, Li Q, Xu Y, Zeng W, et al. Exosomes Mediated Transfer of Circ\_UBE2D2 Enhances the Resistance of Breast Cancer to Tamoxifen by Binding to MiR-200a-3p. *Med Sci Monit Int Med J Exp Clin Res* (2020) 26:e922253. doi: 10.12659/MSM.922253
136. Dou D, Ren X, Han M, Xu X, Ge X, Gu Y, et al. CircUBE2D2 (Hsa\_Circ\_0005728) Promotes Cell Proliferation, Metastasis and Chemoresistance in Triple-Negative Breast Cancer by Regulating miR-512-3p/CDCA3 Axis. *Cancer Cell Int* (2020) 20:454. doi: 10.1186/s12935-020-01547-7
137. Wang L, Zhou Y, Jiang L, Lu L, Dai T, Li A, et al. CircWAC Induces Chemotherapeutic Resistance in Triple-Negative Breast Cancer by Targeting miR-142, Upregulating WWP1 and Activating the PI3K/AKT Pathway. *Mol Cancer* (2021) 20(1):43. doi: 10.1186/s12943-021-01332-8
138. Zheng SR, Huang QD, Zheng ZH, Zhang ZT, Guo GL. Circgfra1 Affects the Sensitivity of Triple-Negative Breast Cancer Cells to Paclitaxel via the miR-361-5p/TLR4 Pathway. *J Biochem* (2021) 169(5):601–11. doi: 10.1093/jb/mvaa148
139. Yan L, Liu G, Cao H, Zhang H, Shao F. Hsa\_circ\_0035483 Sponges hsa-miR-335 to Promote the Gemcitabine-Resistance of Human Renal Cancer Cells by Autophagy Regulation. *Biochem Biophys Res Commun* (2019) 519(1):172–8. doi: 10.1016/j.bbrc.2019.08.093
140. Huang KB, Pan YH, Shu GN, Yao HH, Liu X, Zhou M, et al. Circular RNA Circsnx6 Promotes Sunitinib Resistance in Renal Cell Carcinoma Through the miR-1184/GPCPD1/ Lysophosphatidic Acid Axis. *Cancer Lett* (2021) 523:121–34. doi: 10.1016/j.canlet.2021.10.003
141. Zou FW, Yang SZ, Li WY, Liu CY, Liu XH, Hu CH, et al. circRNA\_001275 Upregulates Wnt7a Expression by Competitively Sponging Mir-370-3p to Promote Cisplatin Resistance in Esophageal Cancer. *Int J Oncol* (2020) 57(1):151–60. doi: 10.3892/ijo.2020.5050
142. Qu F, Wang L, Wang C, Yu L, Zhao K, Zhong H, et al. Circular RNA Circ\_0006168 Enhances Taxol Resistance in Esophageal Squamous Cell Carcinoma by Regulating miR-194-5p/JMJD1C Axis. *Cancer Cell Int* (2021) 21(1):273. doi: 10.1186/s12935-021-01984-y
143. Zhu H, Du F, Cao C. Restoration of Circpsmc3 Sensitizes Gefitinib-Resistant Esophageal Squamous Cell Carcinoma Cells to Gefitinib by Regulating miR-10a-5p/PTEN Axis. *Cell Biol Int* (2021) 45(1):107–16. doi: 10.1002/cbin.11473
144. Zang R, Qiu X, Song Y, Wang Y. Exosomes Mediated Transfer of Circ\_0000337 Contributes to Cisplatin (CDDP) Resistance of Esophageal Cancer by Regulating JAK2 via miR-377-3p. *Front Cell Dev Biol* (2021) 9:673237. doi: 10.3389/fcell.2021.673237
145. Zhang Z, Yu X, Zhou B, Zhang J, Chang J. Circular RNA Circ\_0026359 Enhances Cisplatin Resistance in Gastric Cancer via Targeting miR-1200/POLD4 Pathway. *BioMed Res Int* (2020) 2020:5103272. doi: 10.1155/2020/5103272
146. Deng P, Sun M, Zhao WY, Hou B, Li K, Zhang T, et al. Circular RNA circVAPA Promotes Chemotherapy Drug Resistance in Gastric Cancer Progression by Regulating miR-125b-5p/STAT3 Axis. *World J Gastroenterol* (2021) 27(6):487–500. doi: 10.3748/wjg.v27.i6.487
147. Zhong Y, Wang D, Ding Y, Tian G, Jiang B. Circular RNA Circ\_0032821 Contributes to Oxaliplatin (OXA) Resistance of Gastric Cancer Cells by Regulating SOX9 via miR-515-5p. *Biotechnol Lett* (2021) 43(2):339–51. doi: 10.1007/s10529-020-03036-3
148. Peng L, Sang H, Wei S, Li Y, Jin D, Zhu X, et al. Circul2 Regulates Gastric Cancer Malignant Transformation and Cisplatin Resistance by Modulating Autophagy Activation via miR-142-3p/ROCK2. *Mol Cancer* (2020) 19(1):156. doi: 10.1186/s12943-020-01270-x
149. Huang XX, Zhang Q, Hu H, Jin Y, Zeng AL, Xia YB, et al. A Novel Circular RNA Circfn1 Enhances Cisplatin Resistance in Gastric Cancer via Sponging miR-182-5p. *J Cell Biochem* (2020). doi: 10.1002/jcb.29641
150. Zhang Q, Miao Y, Fu Q, Hu H, Chen H, Zeng A, et al. CircRNACCDC66 Regulates Cisplatin Resistance in Gastric Cancer via the miR-618/BCL2 Axis. *Biochem Biophys Res Commun* (2020) 526(3):713–20. doi: 10.1016/j.bbrc.2020.03.156
151. Huang X, Li Z, Zhang Q, Wang W, Li B, Wang L, et al. Circular RNA AKT3 Upregulates PIK3R1 to Enhance Cisplatin Resistance in Gastric Cancer via miR-198 Suppression. *Mol Cancer* (2019) 18(1):71. doi: 10.1186/s12943-019-0969-3
152. Sun G, Li Z, He Z, Wang W, Wang S, Zhang X, et al. Circular RNA MCTP2 Inhibits Cisplatin Resistance in Gastric Cancer by miR-99a-5p-Mediated Induction of MTMR3 Expression. *J Exp Clin Cancer Res* (2020) 39(1):246. doi: 10.1186/s13046-020-01758-w
153. Liu YY, Zhang LY, Du WZ. Circular RNA Circ-PVT1 Contributes to Paclitaxel Resistance of Gastric Cancer Cells Through the Regulation of ZEB1 Expression by Sponging miR-124-3p. *Biosci Rep* (2019) 39(12):BSR20193045. doi: 10.1042/BSR20193045
154. Xu G, Li M, Wu J, Qin C, Tao Y, He H, et al. Circular RNA Circnrip1 Sponges microRNA-138-5p to Maintain Hypoxia-Induced Resistance to 5-Fluorouracil Through HIF-1 $\alpha$ -Dependent Glucose Metabolism in Gastric Carcinoma. *Cancer Manag Res* (2020) 12:2789–802. doi: 10.2147/CMAR.S246272
155. Sun Y, Ma J, Lin J, Sun D, Song P, Shi L, et al. Circular RNA Circ\_ASAP2 Regulates Drug Sensitivity and Functional Behaviors of Cisplatin-Resistant Gastric Cancer Cells by the miR-330-3p/NT5E Axis. *Anticancer Drugs* (2021) 32(9):950–61. doi: 10.1097/CAD.0000000000001087
156. Liu Y, Xu J, Jiang M, Ni L, Ling Y. CircRNA DONSON Contributes to Cisplatin Resistance in Gastric Cancer Cells by Regulating miR-802/BMI1 Axis. *Cancer Cell Int* (2020) 20:261. doi: 10.1186/s12935-020-01358-w
157. Xu QY, Xie MJ, Huang J, Wang ZW. Effect of Circ MTHFD2 on Resistance to Pemetrexed in Gastric Cancer Through Regulating Expression of miR-124. *Eur Rev Med Pharmacol Sci* (2019) 23(23):10290–9. doi: 10.26355/eurrev\_201912\_19667
158. Wu Q, Wang H, Liu L, Zhu K, Yu W, Guo J, et al. Hsa\_circ\_0001546 Acts as a miRNA-421 Sponge to Inhibit the Chemoresistance of Gastric Cancer Cells via ATM/Chk2/p53-Dependent Pathway. *Biochem Biophys Res Commun* (2020) 521(2):303–9. doi: 10.1016/j.bbrc.2019.10.117
159. Lu Y, Li L, Li L, Wu G, Liu G. Circular RNA Circchectd1 Prevents Diosbulbin-B-Sensitivity via miR-137/PBX3 Axis in Gastric Cancer. *Cancer Cell Int* (2021) 21(1):264. doi: 10.1186/s12935-021-01957-1
160. Gao H, Xu J, Qiao F, Xue L. Depletion of Hsa\_Circ\_0000144 Suppresses Oxaliplatin Resistance of Gastric Cancer Cells by Regulating miR-502-5p/ADAM9 Axis. *Onco Targets Ther* (2021) 14:2773–87. doi: 10.2147/OTT.S281238
161. Liu S, Wu M, Peng M. Circ\_0000260 Regulates the Development and Deterioration of Gastric Adenocarcinoma With Cisplatin Resistance by

- Upregulating MMP11 via Targeting MiR-129-5p. *Cancer Manag Res* (2020) 12:10505–19. doi: 10.2147/CMAR.S272324
162. Wang X, Zhang Y, Li W, Liu X. Knockdown of Cir\_RNA PVT1 Elevates Gastric Cancer Cisplatin Sensitivity via Sponging miR-152-3p. *J Surg Res* (2021) 261:185–95. doi: 10.1016/j.jss.2020.12.013
  163. Yao W, Guo P, Mu Q, Wang Y. Exosome-Derived Circ-PVT1 Contributes to Cisplatin Resistance by Regulating Autophagy, Invasion, and Apoptosis Via miR-30a-5p/YAP1 Axis in Gastric Cancer Cells. *Cancer Biother Radiopharm* (2021) 36(4):347–59. doi: 10.1089/cbr.2020.3578
  164. Xia Y, Lv J, Jiang T, Li B, Li Y, He Z, et al. CircFAM73A Promotes the Cancer Stem Cell-Like Properties of Gastric Cancer Through the miR-490-3p/HMGA2 Positive Feedback Loop and HNRNP-K-Mediated  $\beta$ -Catenin Stabilization. *J Exp Clin Cancer Res* (2021) 40(1):103. doi: 10.1186/s13046-021-01896-9
  165. Liu Y, Xia L, Dong L, Wang J, Xiao Q, Yu X, et al. CircHIPK3 Promotes Gemcitabine (GEM) Resistance in Pancreatic Cancer Cells by Sponging miR-330-5p and Targets Rassf1. *Cancer Manag Res* (2020) 12:921–9. doi: 10.2147/CMAR.S239326
  166. Xu H, Chen R, Shen Q, Yang D, Peng H, Tong J, et al. Overexpression of Circular RNA Circ\_0013587 Reverses Erlotinib Resistance in Pancreatic Cancer Cells Through Regulating the miR-1227/E-Cadherin Pathway. *Front Oncol* (2021) 11:754146. doi: 10.3389/fonc.2021.754146
  167. Yao X, Mao Y, Wu D, Zhu Y, Lu J, Huang Y, et al. Exosomal Circ\_0030167 Derived From BM-MSCs Inhibits the Invasion, Migration, Proliferation and Stemness of Pancreatic Cancer Cells by Sponging miR-338-5p and Targeting the Wif1/Wnt8 $\beta$ -Catenin Axis. *Cancer Lett* (2021) 512:38–50. doi: 10.1016/j.canlet.2021.04.030
  168. Gong J, Luk F, Jaiswal R, George AM, Grau GE, Bebaawy M, et al. Microparticle Drug Sequestration Provides a Parallel Pathway in the Acquisition of Cancer Drug Resistance. *Eur J Pharmacol* (2013) 721(1–3):116–25. doi: 10.1016/j.ejphar.2013.09.044
  169. Joyce H, McCann A, Clynes M, Larkin A. Influence of Multidrug Resistance and Drug Transport Proteins on Chemotherapy Drug Metabolism. *Expert Opin Drug Metab Toxicol* (2015) 11(5):795–809. doi: 10.1517/17425255.2015.1028356
  170. Planells-Cases R, Lutter D, Guyader C, Gerhards NM, Ullrich F, Elger DA, et al. Subunit Composition of VRAC Channels Determines Substrate Specificity and Cellular Resistance to Pt-Based Anti-Cancer Drugs. *EMBO J* (2015) 34(24):2993–3008. doi: 10.15252/embj.201592409
  171. Saxena M, Stephens MA, Pathak H, Rangarajan A. Transcription Factors That Mediate Epithelial-Mesenchymal Transition Lead to Multidrug Resistance by Upregulating ABC Transporters. *Cell Death Dis* (2011) 2(7):e179. doi: 10.1038/cddis.2011.61
  172. Li X, Zhang T. Withdrawn: Circular RNA PTGR1 Regulates 5-FU Resistance and Development of Hepatocellular Carcinoma Cells by Modulating miR-129-5p/ABCC1 Axis. *Cell Biol Int* (2021) 45(11):2391. doi: 10.1002/cbin.11635
  173. Zhao X, Zhong Q, Cheng X, Wang S, Wu R, Leng X, et al. miR-449c-5p Availability Is Antagonized by Circ-NOTCH1 for MYC-Induced NOTCH1 Upregulation as Well as Tumor Metastasis and Stemness in Gastric Cancer. *J Cell Biochem* (2020) 121(10):4052–63. doi: 10.1002/jcb.29575
  174. Chen J, Chen T, Zhu Y, Li Y, Zhang Y, Wang Y, et al. circPTN Sponges miR-145-5p/miR-330-5p to Promote Proliferation and Stemness in Glioma. *J Exp Clin Cancer Res* (2019) 38(1):398. doi: 10.1186/s13046-019-1376-8
  175. Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, et al. The Epithelial-Mesenchymal Transition Generates Cells With Properties of Stem Cells. *Cell* (2008) 133(4):704–15. doi: 10.1016/j.cell.2008.03.027
  176. Milanovic M, Fan DNY, Belenki D, Däbritz JHM, Zhao Z, Yu Y, et al. Senescence-Associated Reprogramming Promotes Cancer Stemness. *Nature* (2018) 553(7686):96–100. doi: 10.1038/nature25167
  177. Shibue T, Weinberg RA. EMT, CSCs, and Drug Resistance: The Mechanistic Link and Clinical Implications. *Nat Rev Clin Oncol* (2017) 14(10):611–29. doi: 10.1038/nrclinonc.2017.44
  178. Dean M, Fojo T, Bates S. Tumour Stem Cells and Drug Resistance. *Nat Rev Cancer* (2005) 5(4):275–84. doi: 10.1038/nrc1590
  179. Schulz A, Meyer F, Dubrovskaya A, Borgmann K. Cancer Stem Cells and Radioresistance: DNA Repair and Beyond. *Cancers (Basel)* (2019) 11(6):862. doi: 10.3390/cancers11060862
  180. Joseph NA, Chiou SH, Lung Z, Yang CL, Lin TY, Chang HW, et al. The Role of HGF-MET Pathway and CCDC66 cirRNA Expression in EGFR Resistance and Epithelial-to-Mesenchymal Transition of Lung Adenocarcinoma Cells. *J Hematol Oncol* (2018) 11(1):74. doi: 10.1186/s13045-018-0557-9
  181. Müller S, Ledl A, Schmidt D. SUMO: A Regulator of Gene Expression and Genome Integrity. *Oncogene* (2004) 23(11):1998–2008. doi: 10.1038/sj.onc.1207415
  182. Maarifi G, Maroui MA, Dutrieux J, Dianoux L, Nisole S, Chelbi-Alix MK, et al. Small Ubiquitin-Like Modifier Alters IFN Response. *J Immunol* (2015) 195(5):2312–24. doi: 10.4049/jimmunol.1500035
  183. Lin YC, Yu YS, Lin HH, Hsiao KY. Oxaliplatin-Induced DHX9 Phosphorylation Promotes Oncogenic Circular RNA CCDC66 Expression and Development of Chemoresistance. *Cancers (Basel)* (2020) 12(3):697. doi: 10.3390/cancers12030697
  184. Shan C, Zhang Y, Hao X, Gao J, Chen X, Wang K, et al. Biogenesis, Functions and Clinical Significance of circRNAs in Gastric Cancer. *Mol Cancer* (2019) 18(1):136. doi: 10.1186/s12943-019-1069-0
  185. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA Circles Function as Efficient microRNA Sponges. *Nature* (2013) 495(7441):384–8. doi: 10.1038/nature11993
  186. Elbarbary RA, Miyoshi K, Myers JR, Du P, Ashton JM, Tian B, et al. Tudor-SN-Mediated Endonucleolytic Decay of Human Cell microRNAs Promotes G(1)/S Phase Transition. *Science* (2017) 356(6340):859–62. doi: 10.1126/science.aai9372
  187. Chen Z, Lu T, Huang L, Wang Z, Yan Z, Guan Y, et al. Circular RNA Ci-MAF Drives Self-Renewal and Metastasis of Liver Tumor-Initiating Cells via Transcription Factor MAFF. *J Clin Invest* (2021) 131(19):e148020. doi: 10.1172/JCI148020
  188. Wesselhoeft RA, Kowalski PS, Anderson DG. Engineering Circular RNA for Potent and Stable Translation in Eukaryotic Cells. *Nat Commun* (2018) 9(1):2629. doi: 10.1038/s41467-018-05096-6
  189. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, et al. Extensive Translation of Circular RNAs Driven by N(6)-Methyladenosine. *Cell Res* (2017) 27(5):626–41. doi: 10.1038/cr.2017.31
  190. Zhang Y, Jiang J, Zhang J, Shen H, Wang M, Guo Z, et al. CircDIDO1 Inhibits Gastric Cancer Progression by Encoding a Novel DIDO1-529aa Protein and Regulating PRDX2 Protein Stability. *Mol Cancer* (2021) 20(1):101. doi: 10.1186/s12943-021-01390-y
  191. Mazumder A, Lee JY, Talhi O, Cerella C, Chateauvieux S, Gaigneaux A, et al. Hydroxycoumarin OT-55 Kills CML Cells Alone or in Synergy With Imatinib or Synribo: Involvement of ER Stress and DAMP Release. *Cancer Lett* (2018) 438:197–218. doi: 10.1016/j.canlet.2018.07.041
  192. Wu J, Chen S, Liu H, Zhang Z, Ni Z, Chen J, et al. Tunicamycin Specifically Aggravates ER Stress and Overcomes Chemoresistance in Multidrug-Resistant Gastric Cancer Cells by Inhibiting N-Glycosylation. *J Exp Clin Cancer Res* (2018) 37(1):272. doi: 10.1186/s13046-018-0935-8
  193. Xu Z, Wang H, Wei S, Wang Z, Ji G. Inhibition of ER Stress-Related IRE1 $\alpha$ /CREB/NLRP1 Pathway Promotes the Apoptosis of Human Chronic Myelogenous Leukemia Cell. *Mol Immunol* (2018) 101:377–85. doi: 10.1016/j.molimm.2018.07.002
  194. Ma XH, Piao SF, Dey S, McAfee Q, Karakousis G, Villanueva J, et al. Targeting ER Stress-Induced Autophagy Overcomes BRAF Inhibitor Resistance in Melanoma. *J Clin Invest* (2014) 124(3):1406–17. doi: 10.1172/JCI70454
  195. Bristol ML, Di X, Beckman MJ, Wilson EN, Henderson SC, Maiti A, et al. Dual Functions of Autophagy in the Response of Breast Tumor Cells to Radiation: Cytoprotective Autophagy With Radiation Alone and Cytotoxic Autophagy in Radiosensitization by Vitamin D 3. *Autophagy* (2012) 8(5):739–53. doi: 10.4161/auto.19313
  196. Sheng Y, Sun B, Xie X, Li N, Dong D. DMH1 (4-[6-(4-Isopropoxyphenyl)Pyrazolo[1,5-a]Pyrimidin-3-Yl]Quinoline) Inhibits Chemotherapeutic Drug-Induced Autophagy. *Acta Pharm Sin B* (2015) 5(4):330–6. doi: 10.1016/j.actpsb.2014.12.010
  197. Smith AG, Macleod KF. Autophagy, Cancer Stem Cells and Drug Resistance. *J Pathol* (2019) 247(5):708–18. doi: 10.1002/path.5222
  198. Tian Y, Yang B, Qiu W, Hao Y, Zhang Z, Yang B, et al. ER-Residential Nogo-B Accelerates NAFLD-Associated HCC Mediated by Metabolic

- Reprogramming of oxLDL Lipophagy. *Nat Commun* (2019) 10(1):3391. doi: 10.1038/s41467-019-11274-x
199. Walker DM, Urbé S, Dove SK, Tenza D, Raposo G, Clague MJ, et al. Characterization of MTMR3. An Inositol Lipid 3-Phosphatase With Novel Substrate Specificity. *Curr Biol* (2001) 11(20):1600–5. doi: 10.1016/s0960-9822(01)00501-2
200. Li H, Xu W, Xia Z, Liu W, Pan G, Ding J, et al. Hsa\_circ\_0000199 Facilitates Chemo-Tolerance of Triple-Negative Breast Cancer by Interfering With miR-206/613-Led PI3K/Akt/mTOR Signaling. *Aging (Albany NY)* (2021) 13(3):4522–51. doi: 10.18632/aging.202415
201. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell* (2011) 144(5):646–74. doi: 10.1016/j.cell.2011.02.013
202. Jiao S, Subudhi SK, Aparicio A, Ge Z, Guan B, Miura Y, et al. Differences in Tumor Microenvironment Dictate T Helper Lineage Polarization and Response to Immune Checkpoint Therapy. *Cell* (2019) 179(5):1177–90.e13. doi: 10.1016/j.cell.2019.10.029
203. Ke B, Wei T, Huang Y, Gong Y, Wu G, Liu J, et al. Interleukin-7 Resensitizes Non-Small-Cell Lung Cancer to Cisplatin via Inhibition of ABCG2. *Mediators Inflamm* (2019) 2019:7241418. doi: 10.1155/2019/7241418
204. Zheng X, Qian Y, Fu B, Jiao D, Jiang Y, Chen P, et al. Mitochondrial Fragmentation Limits NK Cell-Based Tumor Immunosurveillance. *Nat Immunol* (2019) 20(12):1656–67. doi: 10.1038/s41590-019-0511-1
205. Bagchi S, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. *Annu Rev Pathol* (2021) 16:223–49. doi: 10.1146/annurev-pathol-042020-042741
206. Wang Z, Wu X. Study and Analysis of Antitumor Resistance Mechanism of PD1/PD-L1 Immune Checkpoint Blocker. *Cancer Med* (2020) 9(21):8086–121. doi: 10.1002/cam4.3410
207. Zhao R, Ni J, Lu S, Jiang S, You L, Liu H, et al. CircUBAP2-Mediated Competing Endogenous RNA Network Modulates Tumorigenesis in Pancreatic Adenocarcinoma. *Aging (Albany NY)* (2019) 11(19):8484–501. doi: 10.18632/aging.102334
208. Huang Z, Yao F, Liu J, Xu J, Guo Y, Su R, et al. Up-Regulation of circRNA-0003528 Promotes Mycobacterium Tuberculosis Associated Macrophage Polarization via Down-Regulating miR-224-5p, miR-324-5p and miR-488-5p and Up-Regulating CTLA4. *Aging (Albany NY)* (2020) 12(24):25658–72. doi: 10.18632/aging.104175

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**GLOSSARY**

5-FU	5-fluorouracil
ABCB10	ATP binding cassette B family member 10
ADAM28	ADAM metalloproteinase domain 28
ADAM9	ADAM metalloproteinase domain 9
ADM	Adriamycin
AEG-1	Astrocyte-elevating protein-1
AK4	Adenylate kinase 4
AKT	Serine/threonine protein kinase B
ALKBH5	AlkB homolog H5
AML	Acute myeloid leukemia
AMPK	Activated protein kinase
ANLN	Anillin
ARNT2	Aryl hydrocarbon receptor nuclear translocator 2
ARv7	The androgen receptor splicing variant 7
ASAP1	Ankyrin repeat and Pleckstrin homology domain 1
ASK1	Apoptosis signal-regulating kinase 1
ATG2A	Autophagy-related gene 2A
ATG7	Autophagy Related 7
BCL2	B-cell lymphoma-2
BCL-2	B-cell lymphoma-2
BMI1	B cell-specific Moloney murine leukemia virus integration site 1
BRCA1	Breast cancer type 1 susceptibility protein
BTZ	Bortezomib
CAFs	Tumor-associated fibroblasts
CCDC66	Coiled-coil domain containing 66
CCNB1	Cyclin B1
CCNE1	Cyclin E1
CDCA3	Cell division cycle associated 3
CDDP	Cisplatin
CDK4	Cell cycle protein-dependent kinase 4
CDK6	Cyclin-dependent kinase 6
CEBPG	CCAAT enhancer binding protein gamma
CELSR1	Cadherin EGF LAG seven-pass G-type receptors 1
CHD4	Chromodomain helicase DNA-binding protein 4
Chk2	Checkpoint kinase 2
CHTOP	Chromatin target of protein arginine methyltransferase
circRNAs	Circular RNAs
CORO1C	Coronin 1C
CSC	Cancer stem cell
CSPP1	Centrosome and spindle pole associated protein 1
Cul2	Cullin2
CXCL10	Chemokine 10
CXCL12	Chemokine 12
CXCR4	Chemokine receptor type 4 DB
Diosbulbin-B	DCP1A
Decapping enzyme 1a	DDP
Diamminedichloroplatinum	DDP4
Dipeptidyl peptidase-4	DDR
DNA damage response	DDX17
DEAD-box helicase 17	DHX9
DExH-box helicase 9	DONSON
Downstream neighbor of SON	DOX
Doxorubicin	DPP4
Dipeptidyl peptidase 4	DTX
Docetaxel	DUSP7
Dual specificity phosphatase 7	E2F3

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E2F transcription factor 3	ECM
Extracellular matrix	Eg5
Kinesin-5	EGFR
Epidermal growth factor receptor	EIF5A2
Eukaryotic translation initiation factor 5A-2	ELP3
Elongator complex protein 3	EMT
Epithelial-mesenchymal transition	Enz
Enzalutamide	ERK
Extracellular signal-regulated kinase	EZH2
Enhancer of zeste homolog 2	FAM73A
Family with sequence similarity 73	member A
FAT1	FAT atypical cadherin 1
FBXL18	F-box and leucine-rich repeat protein 18
FBXL5	Leucine-rich repeat protein 5
FBXW7	F-box and WD repeat domain containing 7
FGF9	Fibroblast growth factor 9
FGFR1	Fibroblast growth factor receptor 1
FMNL3	Formin like 3
FN1	Fibronectin 1
FOXC2	Forkhead box protein C2
FOXM1	Forkhead box protein M1
FOXO1	Forkhead box O1
FOXO3	Forkhead box O3
FOXO3a	Forkhead box O 3a
Foxp1	Forkhead box protein P1
FOXQ1	Forkhead box Q1
FOXR2	Forkhead box 2
FXR1	Fragile X-Related 1
FZD7	Frizzled-7
GEM	Gemcitabine
GFRA1	GDNF Family Receptor Alpha 1
GLUT1	Glucose transporter 1
GOT1	Glutamate oxaloacetate transaminase 1
GPCPD1	Glycerophosphocholine phosphodiesterase 1
GRB2	Growth factor receptor-bound protein-2
GRK5	G protein-coupled receptor kinase 5
H2AX	Histone family member X
HDGF	Hepatoma-derived growth factor
HECTD1	HECT domain E3 ubiquitin ligase 1
HGF	Hepatocyte growth factor
HIF-1 $\alpha$	Hypoxia-inducible factor-1 $\alpha$
HIPK2	Homeodomain-interacting protein kinase 2
HIPK3	Homeodomain-interacting protein kinase 3
HK2	Hexokinase-2
HMG	High mobility group
HMGA2	High-mobility group AT-hook 2
HMGB1	High-mobility group box 1
HNRNP K	Heterogeneous nuclear ribonucleoprotein K
HOXC8	Homeobox C8
IL-25	Interleukin -25
IM	Imatinib
ITCH	Itchy E3 ubiquitin protein ligase
JAG1	Jagged1
JAK2	Janus kinase 2
JMJD1C	Jumonji domain containing 1C
KANK1	Kidney ankyrin repeat-containing protein 1
KDM4C	Lysine demethylase 4C

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KIF2A	Kinesin family member 2A	PSMC3	Proteasome 26S ATPase subunit 3
KLF12	Krüppel-like factor 12	PTEN	Phosphatase and tensin homolog
LC3	Light chain 3	PTGR1	Effect of prostaglandin reductase 1
LDHA	Lactate dehydrogenase A	PTX	Paclitaxel
LIFR	Leukemia inhibitory factor receptor	PVT1	Plasmacytoma variant translocation 1
LIN28B	Lin-28 homolog B	RAS	Rat sarcoma
m6A	N6-methyladenosine	RASSF1	RAS-Association Domain Family 1
MCTP2	Multiple C2-domains with two transmembrane regions 2	RASSF6	Ras association domain family member 6
MDM2	Mouse double minute 2	RB	Retinoblastoma protein
MDR1	Multidrug resistance gene 1	RBP	RNA binding protein
MDR-1	Multidrug resistance gene-1	REV3L	EV3-like DNA-directed polymerase $\zeta$ catalytic subunit
MECP2	Methyl-CpG-binding-protein 2	RNF	RING finger protein
MEK	Mitogen-activated protein kinase kinase	ROCK	Rho-associated coiled-coil-forming protein kinase
MET	MET proto-oncogene receptor tyrosine kinase	ROR1	Receptor tyrosine kinase-like orphan receptor 1
miRNAs	MicroRNAs	S100A1	S100A1 calcium-binding protein A1
MMP1	Matrix metalloproteinase 1	SAE	SUMO-activating enzyme subunit
MMP11	Matrix metalloproteinase 11	SAE2	Activating enzyme subunit 2
MMP17	Matrix metalloproteinase 17	SCAI	Suppressor of Cancer Cell Invasion
MRP1	Multidrug resistance-associated protein-1	SCMH1	Sex comb on midleg homolog-1
MSH2	MutS homolog 2	SEMA6D	Semaphorins 6D
MSI1	Musashi1	SH2	Src homology region 2
MTA	Pemetrexed	SHP2	SH2-containing protein tyrosine phosphatase 2
MTMR3	Myotubularin-related protein 3	SIK2	Salt inducible kinase 2
MTO1	Mitochondrial tRNA translation optimization 1	SKA1	Spindle and kinetochore-associated complex subunit 1
mTOR	Mechanistic target of rapamycin kinase	SNAI1	Snai family zinc finger 1
MTX	Methotrexate	SNX6	Sorting nexin 6
MutS $\alpha$	Alpha-melanocyte stimulating hormone	SOX4	SRY-box transcription factor 4
MYH9	Myosin heavy chain 9	SOX9	SRY-box transcription factor 9
nAChR $\alpha$ 7	Nicotinic acetylcholine receptor alpha 7	STAT3	Signal transducer and activator of transcription 3
NANOG	Nanog homeobox	STX3	Syntaxin 3
NCOA3	Nuclear receptor coactivator 3	SUMO	Small ubiquitin-related modifier
NEK2	NIMA-related kinase 2	TAM	Tamoxifen
NFIX	Nuclear factor I X	TAMs	Tumor-associated macrophages
NK	Natural killer	TGF- $\alpha$	Transforming growth factor alpha
NRAS	Neuroblastoma RAS	TGM2	Transglutaminase-2
NRIP1	Nuclear receptor-interacting protein 1	TIM-3	T cell immunoglobulin and mucin domain 3
NSCLC	Non-small-cell lung cancer	TKI	Tyrosine kinase inhibitor
NT5E	Ecto-5'-nucleotidase	TKIs	Tyrosine kinase inhibitors
OXA	oxaliplatin	TLR4	Toll-like Receptor 4
PBLD	Problem-based learning discussion	TME	Tumor microenvironment
PBX3	Pre-leukemia transcription factor 3	TMZ	Temozolomide
PD-1	Programmed cell death 1	TNPO3	Transportin3
PK1	3-phosphoinositide-dependent protein kinase 1	TPD52	Tumor protein D52
PD-L1	Programmed death-ligand 1	TRAF4	Tumor necrosis factor receptor associated factor 4
PDPK1	3-phosphatidylinositol-dependent protein kinase-1	TRIM14	Tripartite motif-containing 14
PDX	Patient-derived xenograft	TRIM65	Tripartite motif-containing protein 65
PGAM1	Phosphoglycerate mutase 1	TWIST1	Twist family bHLH transcription factor 1
PI3K	Phosphatidylinositol 3-kinase	UBAP2	Ubiquitin associated protein 2
PI3P	Phosphatidylinositol 3-phosphate	UHRF1	Ubiquitin like with PHD and ring finger domains 1
PIK3R1	The PI3K regulatory subunit p85alpha	ULK1	Unc-51-like kinase 1
PIP5K1A	Phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	USP7	Ubiquitin-specific protease-7
PKM2	The M2 isoform of pyruvate kinase	VapA	Virulence associated protein A
PKP3	Plakophilin 3	VEGFA	Vascular endothelial growth factor A
POLD4	Eukaryote DNA polymerase $\delta$ 4	VRACs	Volume-regulated anion channels
POU3F2	POU class 3 homeobox 2	WIF1	Wnt inhibitory factor 1
PPF1A1	PTPRF interacting protein alpha 1	Wnt7a	Wnt family member 7A
PRDM2	PR/SET domain 2		
PRDX2	Peroxiredoxin 2		
PRKCD	Protein kinase C, delta		
PRPF39	Pre-mRNA splicing factor 39		

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WTAP	Wilms tumor 1-associated protein
XIAP	X-linked inhibitor of apoptosis protein
YAP	Yes-associated protein
YAP1	Yes-associated protein 1
YBX1	Y box binding protein 1
ZEB1	Zinc finger E-box binding homeobox 1
ZIC5	Zinc finger protein of the cerebellum 5