

Serum Hsa_circ_0023919 is a Predictive Biomarker of Chemoresistance in CRC Treatment

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Background: The diversity of available chemotherapeutic modalities for colorectal cancer (CRC) entails the implementation of personalized therapeutic regimens to optimize patient outcomes. Currently, the clinical use of biological markers for treatment selection is inadequate to achieve individualization. Circulatory RNAs (circRNAs), which function as plasma biomarkers, play a critical role in regulating biological processes in different types of cancer.

Methods: The samples (serum) were obtained from 80 CRC patients and 80 healthy individuals (controls) to assess the level of hsa_circ_0023919 via qRT-PCR analysis.

Results: In findings, hsa_circ_0023919 has a positive association with the disease stage and is greatly elevated in chemoresistant CRC patients. In addition, the area under the curve for hsa_circ_0023919 was modest, and an increase in hsa_circ_0023919 expressions was linked with a decreased overall survival (OS) and progression-free survival (PFS). Serum hsa_circ_0023919 levels serve as a diagnostic indicator for chemoresistance in CRC.

Conclusion: The findings suggested that hsa_circ_0023919 contributes to promoting chemoresistance in CRC patients. Consequently, it can be considered a potent therapeutic target for CRC treatment.

Keywords: hsa_circ_0023919, biomarker, chemoresistance, CRC

Introduction

Globally, CRC is listed as the fourth most prevalent cause of cancer-related fatalities.¹ Notably, a new subgroup of unknown cancers of undefined origin (CUP) with good prognosis has recently emerged, which is clinically regarded as CRC, which will help to increase the incidence rate of CRC at present.² Due to the development of multidisciplinary therapeutics, the median overall survival (OS) for CRC has remarkably increased over the last two decades, from 6–12 months to over 30 months.^{3,4} Older CRC patients are more likely to develop severe postoperative complications, but age has no effect on the relative survival rate of T4 stage CRC patients.⁵ Various cytotoxic agents, including anti-angiogenesis inhibitors, irinotecan, anti-epidermal growth factor (EGFR), and fluoropyrimidine (FP), are employed in first-line chemotherapy.⁶

Currently, tumor locations and RAS mutations serve as prognostic indicators for the efficacy of anti-EGFR antibodies, and BRAF mutations are applied as a clinical indicator of poor prognosis, as suggested by the European Society for Medical Oncology (ESMO) recommendation.⁷ Consequently, selecting an appropriate treatment for each patient is critical; moreover, the current clinical implementation of indicators for treatment selection needs to be improved. Thus, the discovery of predictive biomarkers is expected to facilitate treatment decisions that contribute to the improvement of CRC patient management.⁸ The KRAS, NRAS, and BRAF genes or aberrant miRNA may serve as biomarkers for CRC, although an optimal detection and validation strategy is still needed.⁹ The identification of indicators that can predict treatment responses and resistance to the available therapies may facilitate the decision of the highly effective first-line chemotherapeutics for CRC. Biomarkers capable of quantifying the extent of chemoresistance are likewise regarded as valuable tools in the development of suitable treatment approaches, such as adjustments to the treatment. The

detection of these indicators would aid in the understanding of the role of the acquisition of resistance and the development of interventions. The elucidation of the process underlying acquired resistance might act as a basis for the development of drugs for overcoming the resistance.

Circular RNAs (circRNAs), which belong to the family of non-coding RNAs, are abundant in mammalian cells and have been identified in exosomes, body fluids, and tissues.^{10,11} Recently, an increasing body of research has unveiled the discovery that mammalian genomes contain tens of thousands of circRNAs, the dysregulation of which has been the subject of extensive investigation in relation to the development and progression of malignancies.^{12,13} However, additional research is required to determine whether newly identified circRNAs exhibit biological functions in malignancies.

The predominant function of circRNAs in many cancers has been confirmed as the “miRNA sponge” by data from previous studies. Employing sponging miR-140-3p,¹⁴ Hsa_circRNA_0088036 functions as a ceRNA and enhances the progression of bladder cancer. In sponging miR-145 and modulating NRAS,¹⁵ CircRNA_0044556 reduces the susceptibility of triple-negative breast cancer cells to adriamycin. Some circRNAs have been linked to CRC chemoresistance based on a number of previous studies.^{16,17}

The plasma expression patterns of specifically altered circRNAs may function as prognostic or diagnostic indicators.^{18,19} The gene symbol of hsa_circ_0023919 is PICALM, and PICALM is reported to act as a pro-oncogene in CRC.²⁰ It has been noted that serum hsa_circ_0023919 has been implicated in amyotrophic lateral sclerosis as a possible blood biomarker.²¹ However, there is currently no information regarding the possible role of hsa_circ_0023919 in serum as a mediator of chemoresistance in CRC patients. One of the most frequently used first-line chemotherapeutics for CRC patients is combination therapy involving bevacizumab (BEV), FP, and OX. In this study, hsa_circ_0023919 was selected as the prognostic indicator for FP+OX+BEV therapy. Quantitative qRT-PCR was employed to examine the correlation between chemoresistance and the clinical use of hsa_circ_0023919 in CRC patients who were treated with FP+OX+BEV.

Materials and Methods

Sample Collection

In the present study, samples were collected from 80 CRC patients who were treated with the FP+OX+BEV treatment as the initial course of chemotherapy. A CT examination was performed on all patients every three months following chemotherapy to assess chemo-efficacy as per the Response Evaluation Criteria in Solid Tumors.²² In this study, responders were defined as those who obtained a full response, partial response (PR), or reduced stable disease (SD). Non-responders were those who experienced progression disease (PD) or prolonged SD. The Ganzhou People's Hospital gave approval for such an investigation, conducted in line to the Declaration of Helsinki. Investigation participants submitted written informed-consent for specimen gathering.

Rt-Pcr

RNA was isolated from the plasma samples in line with the manufacturer's instructions via the QIAGEN miRNeasy Serum/Plasma Advanced Kit (QIAGEN, Dusseldorf, Germany). The GENEJET RNA purification kit (Fermentas, Lithuania, USA) was utilized to extract RNA from the tissues of the patients as per the recommendation by the manufacturer. Using the Revert Aid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, USA), cDNA was reverse-transcribed from RNA in a 20 µL reaction mixture. qRT-PCR was conducted on an Applied Biosystems ABI Vii7 (Thermo Fisher Scientific, Waltham, USA) utilizing the AceQ Universal SYBR qPCR Master Mix (Vazyme, Nanjing, China). The $2^{-\Delta\Delta Ct}$ method was employed to determine the levels of circRNAs, with GAPDH serving as the control.

Statistical Analysis

Statistical analysis was performed via GraphPad Prism 8.0 (GraphPad, Inc., CA, USA). The data were compared, as appropriate, via Student's *t*-tests and Mann-Whitney tests. A correlation between the plasma circRNA levels and clinical

features was examined by applying the chi-square test. Binary logistic regression analyses were performed in the development of the hsa_circ_0023919 diagnostic model. ROC curve analyses were utilized to identify the most effective cutoff values for plasma circRNA expression, thereby increasing the diagnostic value after ROC curve formation via GraphPad Prism 8.0. The statistical level of significance was represented as a P-value ≤ 0.05 .

Results

Patients Characteristics

The detailed information of the patients who enrolled in this study is listed in Table 1. In this study, approximately 100 participants were recruited, consisting of 38 males and 42 females, and 55 patients were over 60 years old and 25 patients were under 60 years old. There were no significant differences in terms of age, sex, or other demographic data between the CRC patient and volunteer.

CRC Patients Exhibit Elevated Levels of Serum Hsa_circ_0023919

To evaluate the efficacy of hsa_circ_0023919 as a marker of chemoresistance, its concentration in the serum was measured. There was a remarkable increase in serum hsa_circ_0023919 expressions among CRC patients relative to the control group (Figure 1A). Moreover, its expression was higher in patients with chemoresistance (n = 46) as opposed to those with chemosensitivity (n = 34) (Figure 1B).

Association Between Hsa_circ_0023919 Levels and Clinical Manifestations of CRC Patients

The CRC patients were arranged into high and low groups of hsa_circ_0023919 levels in serum, based on the normal expression. In addition, clinical symptoms among both groups were examined. Chi-squared tests revealed a substantial relationship between hsa_circ_0023919 expressions and histological grade, tumor size, and TNM stages (Table 2). Conversely, age, gender, lymph node metastasis, lymphatic invasion, venous invasion, liver metastasis and peritoneal dissemination exhibited a no significant link with hsa_circ_0023919 levels. The Kaplan–Meier assessment indicated that patients with decreased levels of hsa_circ_0023919 have a prolonged OS as opposed to those with increased expression levels (Figure 2).

Table 1 Analysis of the Connection Between Characteristics of Responder and Non-Responder

Item	CRC Patients	Volunteer	p
Number	80	80	
Age			0.521
>60	55	51	
≤60	25	29	
Gender			0.418
Male	38	39	
Female	42	41	
Hyperlipidemia patients	11	10	0.624
Alcohol user	12	10	0.384
Hypertension patients	7	8	0.195
CHD patients	6	5	0.258
Diabetic	3	4	0.571

Abbreviation: colorectal cancer (CRC) and coronary heart disease (CHD).

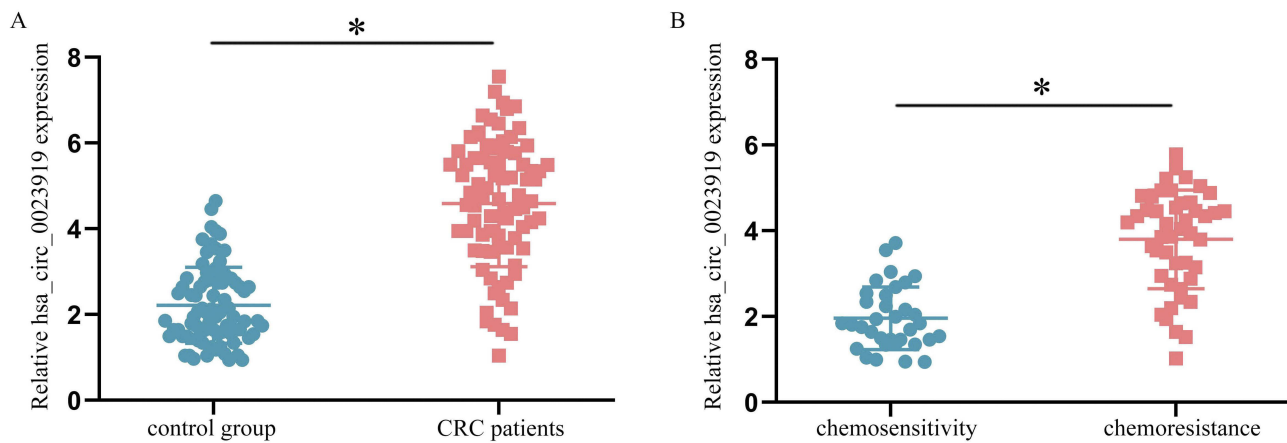


Figure 1 CRC patients revealed high levels of serum hsa_circ_0023919. **(A)** Serum hsa_circ_0023919 levels were elevated in CRC patients. **(B)** Chemoresistant patients displayed elevated levels of hsa_circ_0023919 expressions relative to chemosensitive patients in post-treatment conditions. * $p \leq 0.05$.

Chemoresistant CRC patients with Hsa_circ_0023919 Exhibit a Poor Prognosis

Chemoresistant CRC patients have substantially reduced PFS (Figure 3A) and OS (Figure 3B) than chemosensitive patients, as shown by the Kaplan–Meier and Log rank tests. The significance of this circRNA as a distinct predictor of survival in chemoresistant CRC patients was highlighted by Cox proportional hazards regression analyses that revealed a correlation between hsa_circ_0023919 levels and histological grade, tumor size, TNM stages, and chemoresistance based on patient PFS (Table 3) and OS (Table 4).

Table 2 Comparative Characteristics of Patients with High and Low Expression Levels

Factors	Serum Hsa_circ_0023919		p
	Low Expression	High Expression	
Age			0.524
>60	32	29	
≤60	8	11	
Gender			0.418
Male	21	22	
Female	19	18	
Histological grade			0.015
Well	25	12	
Moderately, poorly	15	28	
Tumor size			0.008
<5 cm (small)	27	11	
>5 cm (large)	13	29	
TNM stages			0.010
I+II	26	12	

(Continued)

Table 2 (Continued).

Factors	Serum Hsa_circ_0023919		p
	Low Expression	High Expression	
III+IV	14	28	
Lymph node metastasis			0.318
Absent	21	20	
Present	19	20	
Lymphatic invasion			0.197
Absent	22	23	
Present	18	17	
Venous invasion			0.219
Absent	25	24	
Present	15	16	
Liver metastasis			0.188
Absent	21	22	
Present	19	18	
Peritoneal dissemination			0.428
Absent	28	24	
Present	12	16	

Level of Serum Hsa_circ_0023919 Serves as a Chemoresistance Diagnostic Index for CRC

To verify the prognostic efficacy of the targeted circRNA in serum, the AUC-ROC was estimated and found to be 0.8977 (95% CI: 0.8303–0.9651, Figure 4, $p \leq 0.0001$). This value is consistent with its potential use as a physiological marker to distinguish between chemosensitivity and chemoresistance.

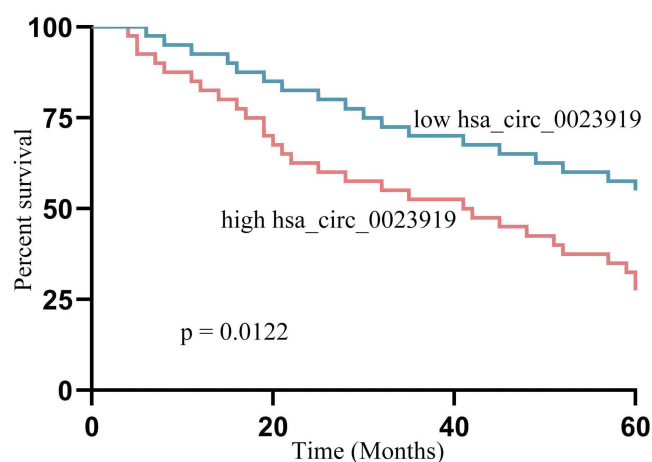


Figure 2 Expressions of hsa_circ_0023919 are linked with the clinical manifestations of CRC patients. Patients who showed elevated hsa_circ_0023919 expression displayed substantially greater OS relative to those with decreased levels.

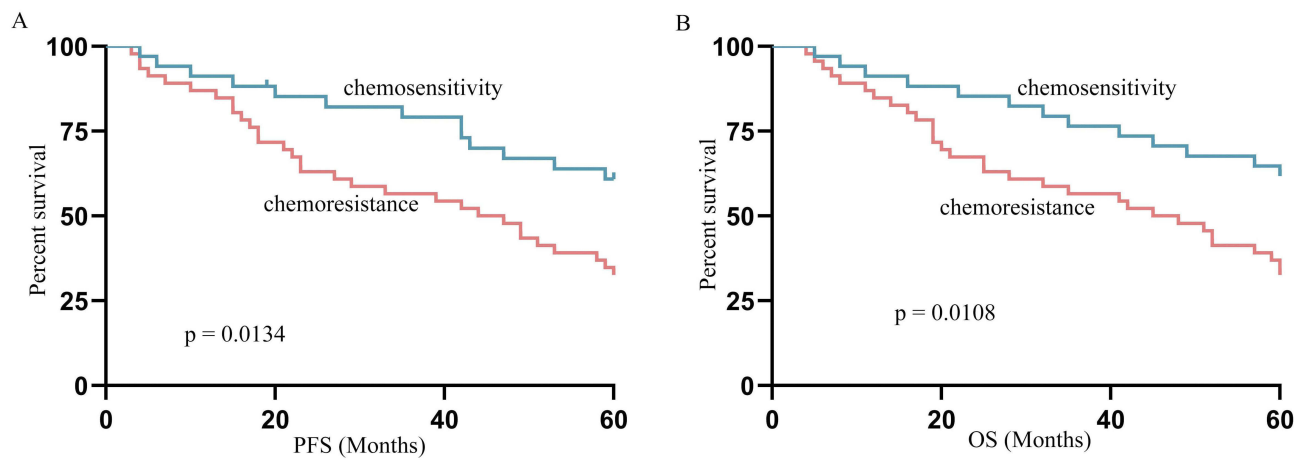


Figure 3 Chemosistant CRC patients with hsa_circ_0023919 have a poor prognosis. In contrast to chemosensitive patients, chemoresistant CRC patients displayed notably reduced (A) PFS and (B) OS.

Discussion

Chemotherapy remains the primary therapeutic approach for CRC, despite the limitations caused by drug resistance.²³ Thus, there is an urgent need to find effective chemotherapeutic biomarkers, such as the importance of microsatellite instability (MSI) and mismatch repair (MMR) detection in predicting CRC patients receiving immunotherapy.²⁴ There is growing evidence indicating that exosomes, which are secreted by various cell types (such as cancer cells), are released into body fluids such as blood, urine, saliva, etc.²⁵ The diverse functions of these exosomes can be attributed to the protein (such as tetraspanins, heat shock proteins, lipid raft proteins, etc), lipid, DNA, and RNA.^{26,27} Furthermore, exosomal RNAs have been involved in tumorigenesis and advancement, epithelial-mesenchymal transition, blood vessel formation, immune response, and therapeutic resistance. Moreover, exosomes transported via bodily secretions may serve as clinical diagnostic biomarkers.²⁸ The gene symbol of hsa_circ_0023919 is PICALM, and PICALM is reported to

Table 3 Two Types of Analyses (Univariate and Multivariate) of the Progression-Free Survival of CRC Patients

Factors	Univariate Analysis		p Value	Multivariate Analysis		p Value
	HR	95% CI		HR	95% CI	
Age (Years)	0.524	0.248–0.954	0.195	–	–	–
Gender	0.418	0.354–0.854	0.243	–	–	–
Histological grade	1.854	0.954–2.458	0.012	1.523	0.876–2.318	0.018
Tumor size	2.015	0.854–2.451	0.011	1.905	0.954–2.541	0.015
TNM stages	2.125	1.021–2.685	0.009	2.104	1.121–2.537	0.013
Lymph node metastasis	0.554	0.325–1.025	0.254	–	–	–
Lymphatic invasion	0.516	0.321–0.858	0.325	–	–	–
Venous invasion	0.654	0.228–0.741	0.218	–	–	–
Liver metastasis	0.491	0.185–0.845	0.341	–	–	–
Peritoneal dissemination	0.374	0.254–0.518	0.297	–	–	–
Hsa_circ_0023919 expression	2.541	1.254–3.021	0.005	2.205	1.002–2.954	0.008
Chemosensitivity	2.415	1.325–2.987	0.008	2.109	1.251–2.854	0.011

Table 4 Two Types of Analyses (Univariate and Multivariate) of the Overall Survival of CRC Patients

Factors	Univariate Analysis		p Value	Multivariate Analysis		p Value
	HR	95% CI		HR	95% CI	
Age (Years)	0.388	0.212–0.619	0.285	–	–	–
Gender	0.395	0.228–0.548	0.194	–	–	–
Histological grade	1.628	0.842–1.888	0.019	1.499	0.748–2.121	0.021
Tumor size	1.842	0.754–2.065	0.015	1.741	0.858–2.169	0.018
TNM stages	2.005	1.025–2.841	0.012	1.869	1.025–2.855	0.014
Lymph node metastasis	0.354	0.254–0.649	0.185	–	–	–
Lymphatic invasion	0.418	0.318–0.852	0.164	–	–	–
Venous invasion	0.518	0.384–0.718	0.218	–	–	–
Liver metastasis	0.396	0.251–0.841	0.319	–	–	–
Peritoneal dissemination	0.645	0.182–0.718	0.208	–	–	–
Hsa_circ_0023919 expression	2.225	1.214–3.185	0.008	2.152	0.954–2.996	0.010
Chemoresistance	2.154	1.125–3.025	0.011	1.959	1.021–2.866	0.013

act as a pro-oncogene in CRC.²⁰ Additionally, in response to a report, serum hsa_circ_0023919 exhibited potential as a blood biomarker in amyotrophic lateral sclerosis.²¹ Thus, hsa_circ_0023919 was selected as the prognostic indicator for FP+OX+BEV therapy.

The significance of circRNA activity in the development of CRC and drug resistance has gradually attracted scientific interest. For instance, hsa_circRNA_102051 inhibits the growth and metastasis of CRC by activating the Notch pathway.²⁹ In CRC, the interaction between CircCAPRIN1 and STAT2 promotes tumor progression and lipid synthesis by increasing ACC1 expression.³⁰ Exosomal circTUBGCP4 enhances CRC metastasis and vascular endothelial cell tipping via triggering the Akt signaling pathway.³¹ These findings demonstrated the significance of circRNAs in CRC drug resistance. In addition, oxaliplatin resistance in CRC is induced by a novel protein encoded by exosomal circATG4B via an enhanced autophagy process.³² In the regulation of the axis, the chemosensitivity of CRC cells to 5-fluorouracil

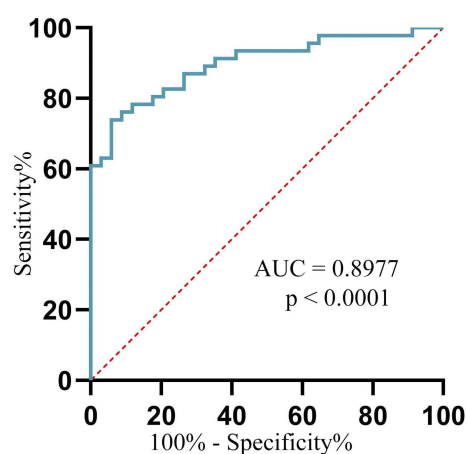


Figure 4 Levels of serum hsa_circ_0023919 serve as a diagnostic indicator for chemoresistance in CRC. To differentiate chemoresistant CRC patients before and following treatment, receiver operating characteristic curves were implemented.

was increased when circ_0004585 was knocked down.³³ Mechanistically, many circRNA can sponge miRNA to regulate mRNA expression, thereby regulating chemotherapy resistance in CRC. For example, circ-CCS regulates oxaliplatin resistance via targeting miR-874-3p/HK2 axis in CRC.³⁴ Circ-CD44 regulates chemotherapy resistance by targeting the miR-330-5p/ABCC1 axis in CRC.³⁵

The efficacy and PFS from FP+OX+BEV chemotherapy were substantially correlated with plasma hsa_circ_0023919 expressions before treatment. Patients who exhibited a favorable response to FP+OX+BEV chemotherapy also had plasma hsa_circ_0023919 expression levels that were correlated with chemoresistance. Recently, several studies have demonstrated a connection between circRNA and chemoresistance in cancer. These studies have also examined circRNA in plasma and serum samples, along with cancer tissues.^{13,36,37} The circRNA is widely recognized for its stability in blood. The circRNAs in the serum or plasma are more feasible to quantify in clinical settings and can be monitored regularly. In relation to chemotherapy resistance, plasma hsa_circ_0023919 was collected from the same patient at various time intervals spanning from before treatment initiation to disease progression or recurrence. This finding implies that plasma hsa_circ_0023919 may serve as a viable molecular indicator for resistance measuring. This was the first investigation that presented plasma circRNA as an FP+OX+BV chemotherapy biomarker.

In conclusion, our findings suggested that the hsa_circ_0023919 expressions in plasma have the potential to serve as a prognostic indicator for assessing the efficiency as a biomarker for chemo-resistance in CRC patients who undergo treatment with the FP+OX+BEV regimen. The overall findings of this study indicated that hsa_circ_0023919 might have a role in the acquisition of resistance, thereby possibly affecting the progress of novel therapeutics for CRC.

Disclosure

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17–48. doi:10.3322/caac.21763
2. Rassy E, Parent P, Lefort F, Boussios S, Baciarello G, Pavlidis N. New rising entities in cancer of unknown primary: is there a real therapeutic benefit? *Crit Rev Oncol Hematol.* 2020;147:102882. doi:10.1016/j.critrevonc.2020.102882
3. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, Phase 3 trial. *Lancet Oncol.* 2014;15(10):1065–1075. doi:10.1016/S1470-2045(14)70330-4
4. Yamazaki K, Nagase M, Tamagawa H, et al. Randomized Phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). *Ann Oncol.* 2016;27(8):1539–1546. doi:10.1093/annonc/mdw206
5. Osseis M, Nehmeh WA, Rassy N, et al. Surgery for T4 Colorectal Cancer in Older Patients: determinants of Outcomes. *J Pers Med.* 2022;12(9):1534. doi:10.3390/jpm12091534
6. Gustavsson B, Carlsson G, Machover D, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. *Clin Colorectal Cancer.* 2015;14(1):1–10. doi:10.1016/j.clcc.2014.11.002
7. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 2016;27(8):1386–1422. doi:10.1093/annonc/mdw235
8. Schirripa M, Lenz HJ. Biomarker in Colorectal Cancer. *Cancer J.* 2016;22(3):156–164. doi:10.1097/PPO.000000000000190
9. Boussios S, Ozturk MA, Moschetta M, et al. The Developing Story of Predictive Biomarkers in Colorectal Cancer. *J Pers Med.* 2019;9(1):12. doi:10.3390/jpm9010012
10. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in Development and Disease: background, Mechanisms, and Therapeutic Approaches. *Physiol Rev.* 2016;96(4):1297–1325.
11. Li Y, Zheng Q, Bao C, et al. Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis. *Cell Res.* 2015;25(8):981–984. doi:10.1038/cr.2015.82
12. Yao B, Zhang Q, Yang Z, et al. CircEZH2/miR-133b/IGF2BP2 aggravates colorectal cancer progression via enhancing the stability of m(6) A-modified CREB1 mRNA. *Mol Cancer.* 2022;21(1):140. doi:10.1186/s12943-022-01608-7
13. Meng X, Xiao W, Sun J, et al. CircPTK2/PABPC1/SETDB1 axis promotes EMT-mediated tumor metastasis and gemcitabine resistance in bladder cancer. *Cancer Lett.* 2023;554:216023. doi:10.1016/j.canlet.2022.216023
14. Yang J, Qi M, Fei X, Wang X, Wang K. Hsa_circRNA_0088036 acts as a ceRNA to promote bladder cancer progression by sponging miR-140-3p. *Cell Death Dis.* 2022;13(4):322. doi:10.1038/s41419-022-04732-w
15. Chen J, Shi P, Zhang J, et al. CircRNA_0044556 diminishes the sensitivity of triple-negative breast cancer cells to Adriamycin by sponging miR-145 and regulating NRAS. *Mol Med Rep.* 2022;25(2):1–2.
16. Wang W, Zhou L, Li Z, Lin G. Circ_0014130 is involved in the drug sensitivity of colorectal cancer through miR-197-3p/PFKFB3 axis. *J Gastroenterol Hepatol.* 2022;37(5):908–918. doi:10.1111/jgh.15829
17. Gao Y, Liu C, Xu X, Wang Y, Jiang Y. Circular RNA sterile alpha motif domain containing 4A contributes to cell 5-fluorouracil resistance in colorectal cancer by regulating the miR-545-3p/6-phosphofructo-2-kinase/fructose-2,6-bisphosphataseisotype 3 axis. *Anticancer Drugs.* 2022;33(6):553–563. doi:10.1097/CAD.0000000000001285

18. Zheng R, Zhang K, Tan S, et al. Exosomal circLPAR1 functions in colorectal cancer diagnosis and tumorigenesis through suppressing BRD4 via METTL3-eIF3h interaction. *Mol Cancer*. 2022;21(1):49. doi:10.1186/s12943-021-01471-y
19. Ge L, Sun Y, Shi Y, et al. Plasma circRNA microarray profiling identifies novel circRNA biomarkers for the diagnosis of ovarian cancer. *J Ovarian Res*. 2022;15(1):58. doi:10.1186/s13048-022-00988-0
20. Zhang X, Liu T, Huang J, He J. PICALM exerts a role in promoting CRC progression through ERK/MAPK signaling pathway. *Cancer Cell Int*. 2022;22(1):178. doi:10.1186/s12935-022-02577-z
21. Dolinar A, Koritnik B, Glavac D, Ravnik-Glavac M. Circular RNAs as Potential Blood Biomarkers in Amyotrophic Lateral Sclerosis. *Mol Neurobiol*. 2019;56(12):8052–8062. doi:10.1007/s12035-019-1627-x
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026
23. Liu C, Zhao Y, Wang J, et al. FoxO3 reverses 5-fluorouracil resistance in human colorectal cancer cells by inhibiting the Nrf2/TR1 signaling pathway. *Cancer Lett*. 2020;470:29–42. doi:10.1016/j.canlet.2019.11.042
24. Adeleke S, Haslam A, Choy A, et al. Microsatellite instability testing in colorectal patients with Lynch syndrome: lessons learned from a case report and how to avoid such pitfalls. *Per Med*. 2022;19(4):277–286. doi:10.2217/pme-2021-0128
25. Ludwig AK, Giebel B. Exosomes: small vesicles participating in intercellular communication. *Int J Biochem Cell Biol*. 2012;44(1):11–15. doi:10.1016/j.biocel.2011.10.005
26. Pan BT, Johnstone RM. Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. *Cell*. 1983;33(3):967–978. doi:10.1016/0092-8674(83)90040-5
27. Boussios S, Devo P, Goodall ICA, et al. Exosomes in the Diagnosis and Treatment of Renal Cell Cancer. *Int J Mol Sci*. 2023;24(18):14356. doi:10.3390/ijms241814356
28. Usman WM, Pham TC, Kwok YY, et al. Efficient RNA drug delivery using red blood cell extracellular vesicles. *Nat Commun*. 2018;9(1):2359. doi:10.1038/s41467-018-04791-8
29. Chen Z, Cheng H, Zhang J, et al. Hsa_circRNA_102051 regulates colorectal cancer proliferation and metastasis by mediating Notch pathway. *Cancer Cell Int*. 2023;23(1):230. doi:10.1186/s12935-023-03026-1
30. Yang Y, Luo D, Shao Y, et al. circCAPRIN1 interacts with STAT2 to promote tumor progression and lipid synthesis via upregulating ACC1 expression in colorectal cancer. *Cancer Commun*. 2023;43(1):100–122. doi:10.1002/cac2.12380
31. Chen C, Liu Y, Liu L, et al. Exosomal circTUBGCP4 promotes vascular endothelial cell tipping and colorectal cancer metastasis by activating Akt signaling pathway. *J Exp Clin Cancer Res*. 2023;42(1):46. doi:10.1186/s13046-023-02619-y
32. Pan Y, Huang Q, Peng X, Yu S, Liu N. Circ_0015756 promotes ovarian cancer progression via the miR-145-5p/PSAT1 axis. *Reprod Biol*. 2022;22(4):100702. doi:10.1016/j.repbio.2022.100702
33. Wang S, Cao J, Pei L. Knockdown of circ_0004585 enhances the chemosensitivity of colorectal cancer cells to 5-fluorouracil via the miR-874-3p/CCND1 axis. *Histol Histopathol*. 2023;38(1):99–112. doi:10.14670/HH-18-502
34. Qiu X, Xu Q, Liao B, Hu S, Zhou Y, Zhang H. Circ-CCS regulates oxaliplatin resistance via targeting miR-874-3p/HK2 axis in colorectal cancer. *Histol Histopathol*. 2023;38(10):1145–1156. doi:10.14670/HH-18-565
35. Zhao S, Xu F, Ji Y, Wang Y, Wei M, Zhang L. Circular RNA circ-CD44 regulates chemotherapy resistance by targeting the miR-330-5p/ABCC1 axis in colorectal cancer cells. *Histol Histopathol*. 2023;38(2):209–221. doi:10.14670/HH-18-516
36. Yang Q, Wu G. CircRNA-001241 mediates sorafenib resistance of hepatocellular carcinoma cells by sponging miR-21-5p and regulating TIMP3 expression. *Gastroenterol Hepatol*. 2022;45(10):742–752. doi:10.1016/j.gastrohep.2021.11.007
37. 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 Non-small Cell Lung Carcinoma. *Cancer Biother Radiopharm*. 2023;38(8):558–571. doi:10.1089/cbr.2020.4490

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