

# World Journal of *Clinical Cases*

*World J Clin Cases* 2021 December 6; 9(34): 10392-10745



**OPINION REVIEW**

- 10392** Regulating monocyte infiltration and differentiation: Providing new therapies for colorectal cancer patients with COVID-19  
*Bai L, Yang W, Qian L, Cui JW*

**REVIEW**

- 10400** Role of circular RNAs in gastrointestinal tumors and drug resistance  
*Xi SJ, Cai WQ, Wang QQ, Peng XC*

**MINIREVIEWS**

- 10418** Liver injury associated with acute pancreatitis: The current status of clinical evaluation and involved mechanisms  
*Liu W, Du JJ, Li ZH, Zhang XY, Zuo HD*
- 10430** Association between celiac disease and vitiligo: A review of the literature  
*Zhang JZ, Abudoureyimu D, Wang M, Yu SR, Kang XJ*
- 10438** Role of immune escape in different digestive tumours  
*Du XZ, Wen B, Liu L, Wei YT, Zhao K*

**ORIGINAL ARTICLE****Basic Study**

- 10451** Magnolol protects against acute gastrointestinal injury in sepsis by down-regulating regulated on activation, normal T-cell expressed and secreted  
*Mao SH, Feng DD, Wang X, Zhi YH, Lei S, Xing X, Jiang RL, Wu JN*

**Case Control Study**

- 10464** Effect of Nephritis Rehabilitation Tablets combined with tacrolimus in treatment of idiopathic membranous nephropathy  
*Lv W, Wang MR, Zhang CZ, Sun XX, Yan ZZ, Hu XM, Wang TT*

**Retrospective Cohort Study**

- 10472** Lamb's tripe extract and vitamin B<sub>12</sub> capsule plus celecoxib reverses intestinal metaplasia and atrophy: A retrospective cohort study  
*Wu SR, Liu J, Zhang LF, Wang N, Zhang LY, Wu Q, Liu JY, Shi YQ*
- 10484** Clinical features and survival of patients with multiple primary malignancies  
*Wang XK, Zhou MH*

**Retrospective Study**

- 10494** Thoracoscopic segmentectomy and lobectomy assisted by three-dimensional computed-tomography bronchography and angiography for the treatment of primary lung cancer  
*Wu YJ, Shi QT, Zhang Y, Wang YL*
- 10507** Endoscopic ultrasound fine needle aspiration *vs* fine needle biopsy in solid lesions: A multi-center analysis  
*Moura DTH, McCarty TR, Jirapinyo P, Ribeiro IB, Farias GFA, Madruga-Neto AC, Ryou M, Thompson CC*
- 10518** Resection of bilateral occipital lobe lesions during a single operation as a treatment for bilateral occipital lobe epilepsy  
*Lyu YE, Xu XF, Dai S, Feng M, Shen SP, Zhang GZ, Ju HY, Wang Y, Dong XB, Xu B*
- 10530** Improving rehabilitation and quality of life after percutaneous transhepatic cholangiography drainage with a rapid rehabilitation model  
*Xia LL, Su T, Li Y, Mao JF, Zhang QH, Liu YY*
- 10540** Combined lumbar muscle block and perioperative comprehensive patient-controlled intravenous analgesia with butorphanol in gynecological endoscopic surgery  
*Zhu RY, Xiang SQ, Chen DR*
- 10549** Teicoplanin combined with conventional vancomycin therapy for the treatment of pulmonary methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections  
*Wu W, Liu M, Geng JJ, Wang M*
- 10557** Application of narrative nursing in the families of children with biliary atresia: A retrospective study  
*Zhang LH, Meng HY, Wang R, Zhang YC, Sun J*

**Observational Study**

- 10566** Comparative study for predictability of type 1 gastric variceal rebleeding after endoscopic variceal ligation: High-frequency intraluminal ultrasound study  
*Kim JH, Choe WH, Lee SY, Kwon SY, Sung IK, Park HS*
- 10576** Effects of WeChat platform-based health management on health and self-management effectiveness of patients with severe chronic heart failure  
*Wang ZR, Zhou JW, Liu XP, Cai GJ, Zhang QH, Mao JF*
- 10585** Early cardiopulmonary resuscitation on serum levels of myeloperoxidase, soluble ST2, and hypersensitive C-reactive protein in acute myocardial infarction patients  
*Hou M, Ren YP, Wang R, Lu LX*

**Prospective Study**

- 10595** Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia  
*Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, Chen C, Liu ZY*

**Randomized Clinical Trial**

- 10604** Effects of lower body positive pressure treadmill on functional improvement in knee osteoarthritis: A randomized clinical trial study  
*Chen HX, Zhan YX, Ou HN, You YY, Li WY, Jiang SS, Zheng MF, Zhang LZ, Chen K, Chen QX*

**SYSTEMATIC REVIEWS**

- 10616** Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease  
*Kan C, Lu X, Zhang R*

**META-ANALYSIS**

- 10626** Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis  
*Chen ZX, Shi Z, Wang B, Zhang Y*

**CASE REPORT**

- 10638** Rarely fast progressive memory loss diagnosed as Creutzfeldt-Jakob disease: A case report  
*Xu YW, Wang JQ, Zhang W, Xu SC, Li YX*
- 10645** Diagnosis, fetal risk and treatment of pemphigoid gestationis in pregnancy: A case report  
*Jiao HN, Ruan YP, Liu Y, Pan M, Zhong HP*
- 10652** Histology transformation-mediated pathological atypism in small-cell lung cancer within the presence of chemotherapy: A case report  
*Ju Q, Wu YT, Zhang Y, Yang WH, Zhao CL, Zhang J*
- 10659** Reversible congestive heart failure associated with hypocalcemia: A case report  
*Wang C, Dou LW, Wang TB, Guo Y*
- 10666** Excimer laser coronary atherectomy for a severe calcified coronary ostium lesion: A case report  
*Hou FJ, Ma XT, Zhou YJ, Guan J*
- 10671** Comprehensive management of malocclusion in maxillary fibrous dysplasia: A case report  
*Kaur H, Mohanty S, Kochhar GK, Iqbal S, Verma A, Bhasin R, Kochhar AS*
- 10681** Intravascular papillary endothelial hyperplasia as a rare cause of cervicothoracic spinal cord compression: A case report  
*Gu HL, Zheng XQ, Zhan SQ, Chang YB*
- 10689** Proximal true lumen collapse in a chronic type B aortic dissection patient: A case report  
*Zhang L, Guan WK, Wu HP, Li X, Lv KP, Zeng CL, Song HH, Ye QL*
- 10696** Tigecycline sclerotherapy for recurrent pseudotumor in aseptic lymphocyte-dominant vasculitis-associated lesion after metal-on-metal total hip arthroplasty: A case report  
*Lin IH, Tsai CH*

- 10702** Acute myocardial infarction induced by eosinophilic granulomatosis with polyangiitis: A case report  
*Jiang XD, Guo S, Zhang WM*
- 10708** Aggressive natural killer cell leukemia with skin manifestation associated with hemophagocytic lymphohistiocytosis: A case report  
*Peng XH, Zhang LS, Li LJ, Guo XJ, Liu Y*
- 10715** Chronic lymphocytic leukemia/small lymphocytic lymphoma complicated with skin Langerhans cell sarcoma: A case report  
*Li SY, Wang Y, Wang LH*
- 10723** Severe mediastinitis and pericarditis after endobronchial ultrasound-guided transbronchial needle aspiration: A case report  
*Koh JS, Kim YJ, Kang DH, Lee JE, Lee SI*
- 10728** Obturator hernia - a rare etiology of lateral thigh pain: A case report  
*Kim JY, Chang MC*
- 10733** Tracheal tube misplacement in the thoracic cavity: A case report  
*Li KX, Luo YT, Zhou L, Huang JP, Liang P*
- 10738** Peri-implant keratinized gingiva augmentation using xenogeneic collagen matrix and platelet-rich fibrin: A case report  
*Han CY, Wang DZ, Bai JF, Zhao LL, Song WZ*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Gagan Mathur, MBBS, MD, Associate Professor, Director, Staff Physician, Department of Pathology, Saint Luke's Health System, Kansas City, MO 64112, United States. gmathur@saint-lukes.org

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yan-Xia Xing, Production Department Director: Yun-Jie Ma, Editorial Office Director: Jin-Lei Wang.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

December 6, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Role of circular RNAs in gastrointestinal tumors and drug resistance

Shi-Jun Xi, Wen-Qi Cai, Qin-Qi Wang, Xiao-Chun Peng

**ORCID number:** Shi-Jun Xi 0000-0003-2434-7722; Wen-Qi Cai 0000-0003-3901-4576; Qin-Qi Wang 0000-0003-1090-3812; Xiao-Chun Peng 0000-0001-9443-0439.

**Author contributions:** Peng XC designed and supervised the study; Xi SJ reviewed the references; Xi SJ and Peng XC wrote the manuscript; Xi SJ, Cai WQ and Wang QQ contributed to tables and figures.

**Conflict-of-interest statement:** The authors declared no conflict of interest.

**Supported by** Natural Science Foundation of Hubei Province, China, No. 2017CFB786; Hubei Province Health and Family Planning Scientific Research Project, China, No. WJ2016Y10; Jingzhou Science and Technology Bureau Project, China, No. 2017-93; the College Students Innovative Entrepreneurial Training Program in Yangtze University, China, No. 2019376; and Postgraduate Innovation Fund Project of Yangtze University, China, No. 200202.

**Country/Territory of origin:** China

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review report's scientific**

**Shi-Jun Xi, Wen-Qi Cai, Qin-Qi Wang, Xiao-Chun Peng,** Department of Pathophysiology, School of Basic Medicine, Health Science Center, Yangtze University, Jingzhou 434023, Hubei Province, China

**Corresponding author:** Xiao-Chun Peng, PhD, Doctor, Department of Pathophysiology, School of Basic Medicine, Health Science Center, Yangtze University, No. 1 Nanhuan Road, Jingzhou 434023, Hubei Province, China. [pxc wd789@sina.com](mailto:pxc wd789@sina.com)

### Abstract

The incidence of gastrointestinal cancers has increased significantly over the past decade and gastrointestinal malignancies now rank among the leading causes of mortality globally. Although newer therapeutic strategies such as targeted therapies have greatly improved patient outcomes, their clinical success is limited by drug resistance, treatment failure and recurrence of metastatic disease. Therefore, there is an urgent need for further research identifying accurate and reliable biomarkers for precise treatment strategies. Circular RNAs (circRNAs) exhibit a covalently closed structure, high stability and biological conservation, and their expression is associated with the occurrence and development of gastrointestinal tumors. Moreover, circRNAs may significantly influence drug resistance of gastrointestinal cancers. In this article, we review the role of circRNAs in the occurrence and development of gastrointestinal cancer, their association with drug resistance, and potential application for early diagnosis, treatment and prognosis in gastrointestinal malignancies. Furthermore, we summarize characteristics of circRNA, including mechanism of formation and biological effects *via* mRNA sponging, chromatin replication, gene regulation, translational modification, signal transduction, and damage repair. Finally, we discuss whether circRNA-related noninvasive testing may be clinically provided in the future. This review provides new insights for the future development of diagnostics and therapeutics based on circRNAs in gastrointestinal tumors.

**Key Words:** Gastrointestinal cancer; Circular RNA; Drug resistance; Genomics; Targeted therapy; Molecular mechanics

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Circular RNAs (circRNAs) were first discovered in 1976, and then more related biological functions were discovered. For example, as a miRNA sponge,

**quality classification**

Grade A (Excellent): 0  
 Grade B (Very good): B  
 Grade C (Good): 0  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Received:** February 7, 2021

**Peer-review started:** February 7, 2021

**First decision:** March 14, 2021

**Revised:** March 26, 2021

**Accepted:** August 5, 2021

**Article in press:** August 5, 2021

**Published online:** December 6, 2021

**P-Reviewer:** Deshwal H

**S-Editor:** Gong ZM

**L-Editor:** Kerr C

**P-Editor:** Guo X



circRNA participates in tumor-related processes, translation modification, signal transduction, and DNA damage repair. Gastrointestinal tumors have a high incidence, and some patients also show drug resistance during treatment. On this basis, we reviewed the relationship between circRNA and gastrointestinal tumors and the relevance of drug resistance, hoping to conduct more in-depth research on circRNA. At the same time, it is hoped that circRNA will provide new directions and strategies for future cancer treatment.

**Citation:** Xi SJ, Cai WQ, Wang QQ, Peng XC. Role of circular RNAs in gastrointestinal tumors and drug resistance. *World J Clin Cases* 2021; 9(34): 10400-10417

**URL:** <https://www.wjgnet.com/2307-8960/full/v9/i34/10400.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v9.i34.10400>

## INTRODUCTION

The incidence of gastrointestinal tumors has increased significantly in recent years[1]. Gastrointestinal tumors, one of the most common cancer types, are increasingly treated with novel treatment strategies including targeted therapies and immunotherapies[2]. In clinical practice, pemetrexed, paclitaxel, cisplatin, sorafenib, and 5-fluorouracil (5-FU), among other drugs, are commonly used therapeutics, but the frequent emergence of drug resistance renders treatment extremely challenging. Radiotherapy and chemotherapy resistance are typically caused by both tumor-cell intrinsic and extrinsic mechanisms, including epithelial-mesenchymal transition (EMT), alterations in tumor microenvironment, and hypoxia signaling[3].

Circular RNAs (circRNAs) have been found to be associated with the occurrence and development of a variety of cancers. They were first detected in 1976 in both RNA viruses and eukaryotic cells[4], but were considered meaningless and an erroneous splicing structure at the time[5]. However, in 1993, Capel *et al*[6] found that circRNAs accounted for > 90% of adult testicular *SRY* transcription. In 2012, Salzman *et al*[7] reported circRNA transcription of hundreds of human genes. Work by Memczak *et al* [8] in 2013 revealed that circRNA exhibit regulatory effects, and later work demonstrated that circRNAs can represent competitive endogenous RNAs[9] (Figure 1). These preliminary studies laid the foundation for the later discovery that circRNA is involved in gastrointestinal tumors. Here, we highlight the relationship between circRNAs and the occurrence and development of gastrointestinal tumors, as well as drug resistance in these tumors.

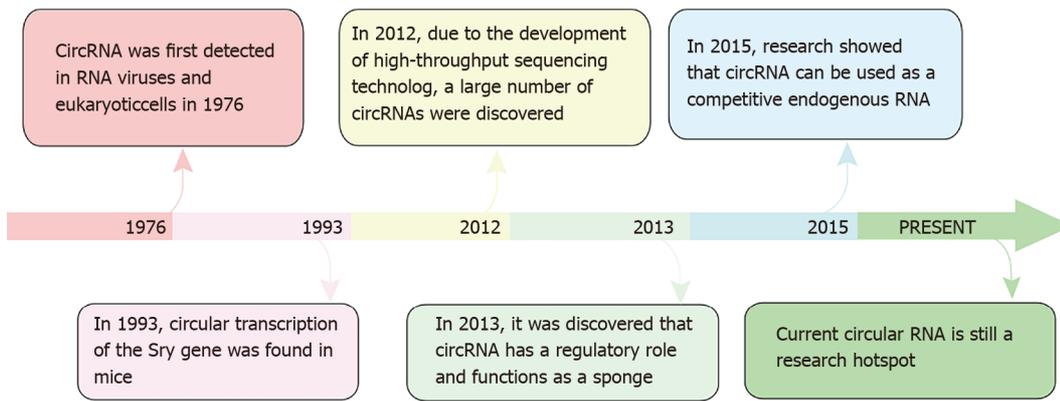
Figure 1 highlights the timeline of breakthrough research on circRNAs and their potential application in the field of oncology.

## INTRODUCTION TO circRNAs

circRNAs have complex biological functions in gastrointestinal tumors. Here, we discuss the sponging effect of circRNAs in tumors as well as their effects on chromatin replication, gene regulation, translational modification, signal transduction, and damage repair.

### Characteristics of circRNAs

circRNAs are circular RNA molecules formed by covalent sealing of single-stranded RNA molecules. The majority of circRNAs is located in the cytoplasm. circRNAs are highly stable and biologically conserved[10]. They have an uncapped 5' end and no polyA structure at the 3' end[11]. circRNAs usually occur during the splicing process after transcription[12], and the majority of circRNAs can be degraded by RNase L endonuclease while they cannot be easily degraded by exonuclease[13]. circRNAs are considered functional noncoding transcripts that can produce functional peptides or proteins[14]: studies have shown that many circRNAs are translated and therefore circRNAs cannot be defined as entirely noncoding RNAs. For example, the 220-nucleotide CCC RNA in the wheat germ extraction system provided the first proof of natural circRNA translation in 2014[15]. Moreover, some circRNAs have an N6-



**Figure 1** The milestones in circRNA research from its discovery in 1976 to present. circRNA: Circular RNA.

methyladenosine (m6A) modification that promotes the translation of circRNAs and plays a role in either inhibition or promotion of tumor progression[16,17]. circRNAs are suggested to be involved in the progression and drug resistance of a variety of cancers, although further studies need to be conducted to confirm the exact mechanisms of action[18]. By understanding the properties and functions of circRNAs, we can further explore the mechanisms of their involvement in gastrointestinal tumors as well as potential future applications for diagnosis and treatment.

### **Mechanisms of circRNA formation**

In recent years, there have been several studies investigating the formation of circRNAs. circRNAs are divided into four types: exonic, intronic, exon-intron, and intergenic[19]. At present, the mechanisms of circRNA processing and maturation are still largely unclear[20], but recent studies suggest that 80% of circRNAs are exonic circRNAs (ecircRNA), which have two key formation mechanisms: lasso-driven circularization (exon skipping) and intron pair-driven circularization (direct reverse splicing)[21] (Figure 2). mRNA intron lassos can evade degradation during splicing, forming circRNA with 2', 5'phosphodiester bonds, and the same sequence can form different circRNAs *via* different types of splicing. Not all exons can be spliced to form circRNAs, however the more spliced an RNA is, the less fully processed mRNA exists, for example in the rat *P4502C24* gene[22].

There are also other theories that state that circRNAs can be formed by RNA-binding proteins (RBPs) or flanking introns that interact with each intron through RNA-RNA interaction to promote the combination of both ends of the head and tail, ultimately leading to the formation of intronic circRNAs (ciRNAs) or exon-intron circRNAs (EiRNAs). More research investigating the formation mechanisms of circRNA in-depth will thus be required in the future.

### **Biological function of circRNAs**

**circRNA sponge effects:** circRNAs are associated with various conditions and diseases including aging, defect insulin secretion, Alzheimer’s disease, gastrointestinal tumors, as well as cardiovascular and cerebrovascular diseases, to name a few[23-26]. Generally, circRNAs bind to mRNAs by base complementary pairing, thereby potentially participating in the tumor related processes[27].

CDR1as is the product of cerebellar degeneration-related protein 1 (CDR1), also known as ciRS-7[28]. Knockdown of CDR1as can promote the degradation of miR-7-targeted mRNA and can act as a miR-7 sponge[29,30]. It has been reported that in addition to ciRS-7, circPVT1 may also promote cell proliferation by acting as a sponge for miR-125 family members[31]. circRNAs can also act as sponges for RBPs or miR-138 family members[32,33].

circRNAs exhibit a sponging activity for specific miRNAs, thereby inhibiting miRNA-based inhibition of gene expression.

**Impact of circRNAs on chromatin replication:** Increasing numbers of studies have shown that circRNAs are involved in chromatin replication. Chromatin replication includes DNA and nucleosome replication, during which nucleosomes interact with nucleoproteins that are important for protein recruitment, DNA replication, transcription, and damage repair[34]. DNA replication occurs in the nucleus[35]. During chromatin replication, certain proteins may be recruited which help to

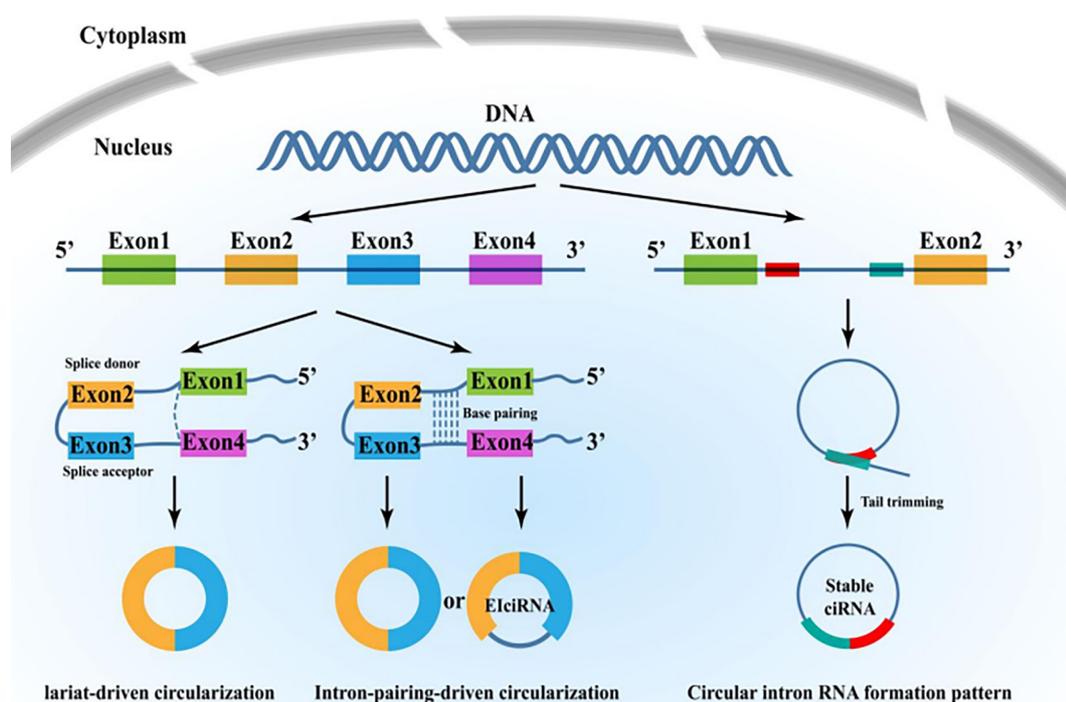


Figure 2 Four mechanisms of circular RNA formation including exonic circular RNA, intronic circular RNA, exon-intron circular RNA, intergenic circular RNA.

organize chromatin regions and regulate gene expression. Chromatin immunoprecipitation (ChIP) sequencing technology has detected the presence of nuclear circRNAs during chromatin replication, which indicates that circRNAs may play a role in this process[36]. Moreover, ChIP studies have also found that overexpression of circRNAs inhibits tumor proliferation in bladder cancer[37]. Clarifying the role of circRNAs in chromatin replication may therefore provide future insights for inhibiting tumor proliferation.

**CircRNA regulation of gene transcription:** circRNAs regulate gene transcription function and play an important role in gastrointestinal tumors. Studies have shown that addition of m6A is a reversible transcriptomic modification found in many eukaryotic mRNAs[38]. m6A modification of circRNAs aids their translation to proteins[39,40]. For example, circ-FBXW7 can be translated into the FBXW7-185aa protein after m6A modification[14]. Circular structures may even be translated into more proteins than linear structure in the ribosome[41]. circRNAs are transcribed by RNA polymerase (Pol) II and can be produced by spliceosomes, including heterogeneous nuclear ribonucleoproteins (hnRNPs)[42]. For example, when precipitating circEIF3J or circPAIP2, PolII, U1A, U1c and U1 small nuclear RNAs are detected. Similarly, ElciRNAs can interact with Pol II, U1 hnRNP and parental gene promoters to enhance the transcription of parent genes, thus affecting protein translation[43]. The peptides encoded by circRNA can interfere with the metabolism or metastasis of tumors, thereby exerting an antitumor effect[44]. Nuclear circRNAs act as transcriptional or splicing regulators that interfere with gene expression and participate in selective splicing and transcription processes[45]. For instance, circITGA7 plays a negative regulatory role in the Ras pathway and inhibits *RREB1* upregulation through the Ras pathway, which typically results in *ITGA7* transcription[46]. circSHKBP1 has been shown to act as a miR-582-3p sponge and regulates the HUR/VEGF pathway in the promotion of the progression of gastric cancer[47].

To summarize, circRNAs play many biological roles and are involved in splicing, transcriptional or translational regulation, sequestering of miRNA, and protein binding. Although the mechanisms are largely unclear, circRNAs are likely to play a vital role in tumor development *via* these processes.

**circRNA post-translational modifications (PTMs):** Modifications can be regulated by the structure of chromatin, and it can also use ATP hydrolysis to generate energy to relocate the recombinase, and post-translational histone modifications, such as acetylation, phosphorylation, methylation and many other forms[48]. PTMs often

occur after protein translation. The most common PTMs influenced by circRNAs are methylation and acetylation. In the tumor microenvironment, circRNAs can promote acetylation and kill tumor cells by regulation of gene expression. For example, circSETD3 can inhibit  $\alpha$ -tubulin acetylation by upregulation of *MAPER1* expression in nasopharyngeal carcinoma, thereby promoting the invasion and migration of tumor cells, confirming a potential for circRNAs as a biomarker[49]. In gastric cancer, circMRPS35 can inhibit the progression of tumors *via* the circMRPS35/KAT7/foxo1/3a pathway, influencing acetylation *via* the histone acetyltransferase KAT7[50]. In liver cancer, circRNAs have been shown to modify methylation, with most circRNAs with methylation sites having only one methylation peak[51]. Moreover, circSOD2 increases the DNA methylation of the SOCS3 promoter, thereby playing a role in liver cancer tumors[52].

**circRNAs and signal transduction:** Signal transduction pathways often undergo abnormal changes in the occurrence and development of tumors. In osteosarcoma, circTCF25 has been shown to promote phosphorylation of signal transducers and produce carcinogenic effects[53]. In lung cancer, circ-ZKSCAN1/miR-330-5p/FAM83A can regulate the signal transduction pathway, and the reduction of circ\_ZKSCAN1 can inhibit tumor cell migration and proliferation[54]. In breast cancer, hsa-circ-0061825 (circ-TFF1) may promote progression by affecting miR-326/TFF1 signaling[55]. circFMN2 may promote colorectal cancer progression *via* the miR-1182/hTERT signaling pathway[56]. circ0000190 has been shown inhibit proliferation and metastasis of gastric cancer cells by regulation of caspase-3 expression and inhibition of the miR-1252/PAK3 pathway[57]. Exploring diverse signaling pathways influenced by circRNA may provide potential therapeutic targets relating to tumor development and progression in the future.

**circRNAs and damage repair:** DNA breaks are characterized as single- or double-strand [58]. *In vivo* repair mechanisms support the precise repair of single-strand breaks, while double-strand breaks often lead to cell death[59]. The occurrence of tumors is sometimes related to radiation, which causes DNA double-strand breaks. In noncoding RNA, the signal ionizing radiation response can be adjusted by targeting [60]. In breast cancer, circSMARCA5 can participate in the remodeling of damaged chromatin DNA[61]. Assessing the influence of circRNAs on DNA damage repair mechanisms in different cells may provide valuable information for DNA repair in the future.

## circRNAs AS BIOMARKERS AND THERAPEUTIC TARGETS IN GASTROINTESTINAL TUMORS

Tumor development is a complicated pathological process. Molecules such as noncoding RNAs and cell-free DNA may be used as potential biomarkers but also therapeutic targets for benign and malignant diseases of the gastrointestinal tract[62]. The mechanism of anticancer drug resistance is multifaceted. Tumor growth, tumor microenvironment, immune system, and selective treatment pressure all affect tumor resistance[63]. Unfortunately, some patients develop drug resistance that requires exploration of other treatment directions. Therefore, drug resistance research is a key area of investigation. Several studies have suggested that circRNAs may play a key role not only as therapeutic targets for digestive system tumors but targeting them may also help to overcome drug resistance.

### **circRNAs regulate gastric cancer progression and drug resistance**

Owing to their special circular structure, circRNAs can be stably present in peripheral bodily fluids such as saliva and plasma, and can remain stable in serum for > 24 h[64]. Research has found that out of 11 circRNAs assessed, five were upregulated and promoted cancer, while six were downregulated and exhibited cancer-suppressing effects[65].

circRNA100876 is highly expressed in gastric cancer (GC) tissues and influences the miR-665/YAP1 signaling pathway. It can inhibit the proliferation, invasion and migration of GC cells by downregulation of the EMT pathway[66]. Conversely, studies have shown that circCUL3 can promote extracellular acidification rate, lactic acid production, and GC cell proliferation. This circRNA is highly expressed in GC tumor cells and has been shown to promote the expression of signal transducer and activator

of transcription (STAT) 3 *via* sponging of miR-515-5p[67]. Similarly, circTMEM87A is also highly expressed in GC and can sponge miR-142-5p, regulating ULK1 expression and thus promoting GC proliferation and metastasis[68]. circRNA-0044516 is likewise upregulated in GC and acts as a miR-149 sponge. circRNA-0044516 silencing results in reduced Wnt1 and  $\beta$ -catenin protein levels and inhibits GC progression[69]. circ0000039 is also upregulated in GC, adsorbs miR-1292-5p, and upregulates *DEK* expression to promote GC proliferation and progression as an oncogene[70]. Circ-0004872 is significantly downregulated in GC tumor cells and has a tumor-suppressive effect. It acts as a miR-224 sponge and upregulates expression of miR-224 downstream targets p21 and Smad4[71]. circ-ITCH is also lowly expressed in GC. It negatively regulates the Wnt/ $\beta$ -catenin signaling pathway as a tumor suppressor, inhibiting tumor occurrence and development[72]. circPDZD8 is an oncogene circRNA that is upregulated in GC tissues and cells and acts as a miR-197-5p sponge. Its knockout is beneficial for suppression of tumor occurrence[73].

circRNAs participate in various pathological processes. However, their participation in processes such as drug resistance is not mediated by simple up- or downregulation. Their special covalent closed-loop structures play biological roles in transcription and translation and these mechanisms need to be further explored and characterized. Studies have shown that circMTHFD2 can promote GC cell resistance to pemetrexed *via* molecular sponging of miR-124, thereby increasing the patient's medication time for pemetrexed, reducing the occurrence of drug resistance, and prolonging patient survival[74]. circ-PVT1 enhances the sensitivity of GC cells to paclitaxel by negatively regulating miR-124-3p, and its knockdown increases the sensitivity of gastric cancer to paclitaxel[75]. circAKT3 promotes DNA damage repair both *in vivo* and *in vitro* and inhibits apoptosis in GC patients. Moreover, circAKT3 promotes *PIK3R1* expression *via* miR-198 targeting, and circAKT3 downregulation, which is conducive to the cisplatin sensitivity of GC cells, indicating that circAKT3 knockdown inhibits further growth of GC, improves GC sensitivity and prolongs survival of patients using cisplatin drugs [76]. circFN1 (hsa-circ-0058147) is predominantly located in the cytoplasm and regulates cisplatin activity *via* miR-182-5p targeting, preventing the ability of miR-182-5p to activate caspase-3 *via* phosphorylation and inhibition of apoptosis in GC patients. Several studies point towards an involvement of circFN1 in cisplatin resistance and it may represent a future therapeutic target for cisplatin resistance in patients with GC[77]. circRNA may play a role in GC through regulating signaling pathways, and have an impact on the development of drug resistance in these GC patients. The specific mechanisms need to be further studied, but given the evidence so far, the role of circRNAs in GC should not be underestimated. Thus, circRNAs may play an important role as a potential diagnostic and prognostic indicators of GC in the future (Table 1).

### **circRNAs regulate liver cancer progression and drug resistance**

Hepatocellular carcinoma (HCC) has become one of the leading global cancers with an extremely high fatality rate. The prevalence of liver cancer is higher in men than in women, and it is related to risk factors such as hepatitis B and C, smoking, diabetes, and *Aspergillus* infections[78]. Studies have demonstrated that several circRNAs may either be potential biomarkers for the diagnosis of HCC or represent therapeutic targets for inhibiting tumor development. For example, hsa-circ-0004018 is highly sensitive to  $\alpha$ -fetoprotein and circ-0016788 may represent a personalized treatment for HCC patients[79]. Similarly, circZKSCAN1 and circPCNX may be used as diagnostic markers for liver cancer[80], while hsa-circRNA-100084 acts as a sponge for hsa-miR-23A-5P, promoting *IGF2* expression[81]. circ-0051443 is transferred from normal cells to cancer cells *via* exosomes and exerts tumor-suppressing functions, inhibiting HCC [82]. circ-0091579 suppresses HCC proliferation and metastasis *via* targeting miRNA-490-3p. circABC10 acts as a miR-670-3p sponge, upregulating *HMG20A* expression and thereby promoting HCC development. However, circABC10 knockdown inhibits the migration and metastasis of tumor cells[83]. The mechanisms of action of circRNAs in liver cancer need to be further investigated to achieve better insights regarding their role and therapeutic potential.

Patients with liver cancer often face drug resistance. circRNAs have been found to influence drug resistance in several studies. For example, circRNA-101237 is associated with cisplatin sensitivity in HCC patients. Increased levels of circRNA101237 have been reported in the serum of cisplatin-resistant HCC patients and Huh7 cells, and patients with high expression typically have poor prognosis and low survival rates. circRNA\_101237 can be used as an independent predictor of the prognosis of liver cancer patients[84]. hsa-circ-u0006294, hsa-circ-u0035944 and hsa-circ-u0084663 activate the Wnt/ $\beta$ -catenin pathway and inhibit HCC growth; of these, hsa-circ-

**Table 1** circRNAs involved in gastric cancer gene transcription regulation and drug resistance

Cancer species	circRNA	Gene expression		Mechanism	Drug	Ref.
		Up	Down			
Gastric cancer	circRNA100876	↑		Via miR-665/YAP1 signaling pathway	NR	[66]
Gastric cancer	circCUL3	↑		Acts as a sponge for miR-515-5p	NR	[67]
Gastric cancer	circTMEM87A	↑		Acts as a sponge for miR-142-5p	NR	[68]
Gastric cancer	circRNA0044516	↑		Acts as a sponge for miR-149	NR	[69]
Gastric cancer	circ0000039	↑		Acts as a sponge for miR-1292-5p	NR	[70]
Gastric cancer	has-circ-0004872		↓	Acts as a sponge for miR-224	NR	[71]
Gastric cancer	circ-ITCH		↓	Negative regulation of Wnt/ $\beta$ -catenin signaling pathway	NR	[72]
Gastric cancer	circPDZD8	↑		Acts as a sponge for miR-197-5p	NR	[73]
Gastric cancer	circMTHFD2	↑		Combined with miR-124 to exert sponge effect and induce MDR-1 protein	Pemetrexed	[74]
Gastric cancer	circ-PVT1	↑		By negatively regulating miR-124-3p	Paclitaxel	[75]
Gastric cancer	circAKT3	↑		Promote PIK3R1 expression through miR-198	Cisplatin	[76]
Gastric cancer	circFhashsa-circ-0058147	↑		Regulation of cisplatin activity <i>via</i> miR-182-5p	Cisplatin	[77]

NR: Not reported; circRNA: Circular RNA.

u0006294 and hsa-circ-u0035944 have been found to be downregulated in HCC and influence sorafenib resistance[85]. Likewise, circ-0003418, which inhibits the Wnt/ $\beta$ -catenin pathway, is downregulated in HCC, but increases the sensitivity of HCC to cisplatin. Conversely, knocking down circ-0003418 promotes HCC growth and proliferation[86]. circFBXO11 is upregulated in HCC and promotes progression and oxaliplatin resistance *via* the miR-605/FOXO3/ABCB1 axis[87].

Liver resection and liver transplantation are common surgical treatments for patients with liver cancer[88]. Patients usually require radiotherapy and chemotherapy after surgical resection. However, with chemotherapy and targeted medication, drug resistance often occurs and the probability of liver cancer recurrence is high with poor prognosis. As presented in the results above, circRNAs have been shown to regulate HCC tumor growth, differentiation, apoptosis and migration. These and future studies may enable the application of circRNAs as potential prospective biomarkers in liver cancers, and the above-mentioned circRNAs may also have certain regulatory effects on drug resistance. Further in-depth research will likely provide new diagnostic indicators for liver cancer patients (Table 2).

### ***circRNAs regulate colorectal cancer progression and drug resistance***

Colorectal cancer (CRC) is the third most deadly and fourth most commonly diagnosed cancer in the world. Alcohol, tobacco, sedentary lifestyles and obesity have been reported to increase the risk of CRC[89]. It is estimated that by 2030, the global incidence of CRC will be as high as 60%, meaning that there will be nearly 1.4 million new patients[90]. Many circRNAs are dysregulated in CRC tissues compared with the normal mucosa. circNSUN2 is opposite to the 5p15 amplicon and interacts with *YTHDC1*, *SRSF3*, and *NXF1*. Upregulation of circNSUN2 in CRC promotes metastasis and is associated with poor prognosis; as a cancer-promoting circRNA, it may be used as a clinical diagnostic or prognostic marker in the future[91]. hsa-circ-101555 (circ101555) is also a cancer-promoting circRNA that sponges miR-597-5p, whose potential targets are *CDK6* and *RPA3*. hsa-circ-101555 knockdown results in inhibition of CRC proliferation and metastasis, thus it may also be used as a future prognostic factor and therapeutic target for CRC[92]. High levels of circHIPK3 expression result in a low overall survival rate of CRC, and there is a negative correlation between circHIPK3 expression and CRC survival. circHIPK3 can inhibit the proliferation, migration and invasion of CRC cells[93]. circCCDC66 exerts its function by regulation of a subset of oncogenes, and studies have shown that circCCDC66 knockout inhibits CRC cell growth and invasion, while circCCDC66 upregulation results in poor CRC

Table 2 circRNAs involved in liver cancer gene transcription regulation and drug resistance

Cancer type	circRNA	Gene expression		Mechanism	Drug	Ref.
		Up	Down			
Liver cancer	circ100084	↑		Promotes IGF2 expression by acting as a sponge for HSA-MIR-23A-5P	NR	[81]
Liver cancer	circABCB10	↑		Upregulates HMG20A expression by acting as a miR-670-3p sponge	NR	[83]
Liver cancer	circRNA-101237	↑		Increased levels in serum and Huh7 cells of cisplatin-resistant HCC patients	Cisplatin	[84]
Liver cancer	Hsa-circ-u0006294, hsa-circ-u0035944, hsa-circ-u0084663		↓	Plays a role by activating the Wnt/ $\beta$ -catenin pathway	Sorafenib	[85]
Liver cancer	circ-0003418		↓	Inhibits Wnt/ $\beta$ -catenin pathway	Cisplatin	[86]
Liver cancer	circFBXO11	↑		Uses miR-605 /FOXO3/ABCB1 axis adjustment	Oxaliplatin	[87]

NR: Not reported; circRNA: Circular RNA.

prognosis. Additionally, circCCDC66 knockdown increases the therapeutic effect of oxaliplatin on CRC[94,95]. hsa-circ-0000069 is highly expressed in CRC and its knockdown significantly inhibits the growth and proliferation of tumor cells[96].

In addition to their roles in both suppression and promotion of cancer, circRNAs also play a key role in drug resistance. Topoisomerase is widely distributed in eukaryotic cells and was identified as the target of the anticancer drug camptothecin in the 1970s. Irinotecan, a camptothecin derivative, is used as a treatment for CRC. It is an S-phase-specific, effective anticancer treatment for metastatic CRC. circRNAs may promote irinotecan resistance by regulating cancer-stem-cell-like characteristics[97]. For example, circ001680 modulates *BMI1* via miR-340 and it can be used to induce irinotecan sensitivity in CRC, suppressing CRC proliferation and migration. circ001680 may thus represent a potential indicator of irinotecan chemotherapy resistance[98]. hsa-circ-0005963 inhibits glycolysis and reverses drug resistance by targeting *pKM2* via miR-122 sponging: it increases oxaliplatin sensitivity in CRC via downregulation of PKM2[99]. circ-0000338, which is found in extracellular vesicles, has been found to improve 5-FU resistance in CRC cells. circ-0000338 may have dual regulatory effects, capable of both suppressing and causing cancer[100]. hsa-circ-32883 expression is upregulated in CRC, and the circRNA produced by the exon region exerts a cancer-promoting effect. Thus, hsa-circ-32883 may be a powerful biological target, but its mechanism of resistance relating to 5-FU and oxaliplatin is not yet clear[101]. The expression of circ0007031, circ0000504 and circ0007006 is elevated in CRC. Upregulation of hsa-circ-0000504 can reduce the inhibitory effect of hsa-miR485-5p on STAT3 and promotes chemical radiation resistance. Additionally, silencing STAT3 results in a significant reduction of 5-FU resistance and clone survival after irradiation[102]. hsa-circ-0079662 regulates *HOXA9* and induces oxaliplatin resistance via hsa-miR-324-5p binding in CRC[103]. Studies have shown that circDDX17 can enhance CRC sensitivity to 5-Fu via upregulation of miR-31-5p/KANK1[104].

Taken together, circRNAs appear to play important roles in CRC which is summarized in Table 3.

### **circRNAs regulate esophageal cancer progression and drug resistance**

Esophageal cancer (EC) is an extremely aggressive type of cancer with a 5-year survival rate between 15% and 20%. EC is the eighth most prevalent tumor in the world and the sixth leading cause of cancer-related deaths. Due to its poor prognosis and low survival rate, it is particularly important to identify the reliable biomarkers for its early diagnosis[105].

A study has reported 1045 upregulated and 1032 downregulated circRNAs in EC [106], and several studies have suggested that circRNAs play an important role in the regulation of gene transcription in EC. For example, hsa-circ-0004771 promotes esophageal squamous cell carcinoma via the miR-339-5P/CDC25A axis, and its knockdown inhibits proliferation and migration of development of esophageal squamous-cell carcinoma (ESCC). Nonetheless, its mechanisms of action have not been

**Table 3 circRNAs involved in colon cancer gene transcription regulation and drug resistance**

Cancer type	circRNA	Gene expression		Mechanism	Drug	Ref.
		Up	Down			
Colon cancer	circNSUN2	↑		Interact with YTHDC1, SRSF3 and NXF1	NR	[91]
Colon cancer	hsa-circ-101555	↑		Acts as miR-597-5p sponge	NR	[92]
Colon cancer	circHIPK3	↑		Acts as miR-7 sponge	NR	[93]
Colon cancer	circCCDC66	↑		DHX9 phosphorylation	Oxaliplatin	[94,95]
Colon cancer	circ-001680	↑		Adjust BMI1 <i>via</i> miR-340	Irinotecan	[98]
Colon cancer	hsa-circ-0005963	↑		Acts as miR-122 sponge	Oxaliplatin	[99]
Colon cancer	circ-0000338	↑	or ↓	Knock out circ-0000338 improves drug resistance	5-FU	[100]
Colon cancer	hsa-circ-32883	↑		uncertain	5-FU, oxaliplatin	[101]
Colon cancer	circ0007031, circ0000504, circ0007006	↑		Use hsa-miR485-5p pathway	5-FU	[102]
Colon cancer	hsa-circ-0079662	↑		Using the TNF- $\alpha$ pathway	oxaliplatin	[103]
Colon cancer	circDDX17	↑		Adjustable <i>via</i> miR-31-5p/KANK1 axis	5-FU	[104]

NR: Not reported; circRNA: Circular RNA.

fully elucidated[107]. circUBAP2 is upregulated in ESCC and acts as a miR-422a sponge. circUBAP2 knockdown inhibits ESCC progression and prevents the spread of tumor cells[108]. hsa-circ-0006948 is likewise upregulated in ESCC and promotes the growth and development of tumor cells *via* the miR-490-3p/HMGA2 axis[109]. Similarly, circ-0000654 is upregulated in ESCC. It promotes proliferation and migration of tumor cells *via* the miR-149-5p/IL-6/STAT3 axis and tumor progression can be suppressed by circ-0000654 knockdown[110]. circGSK3 is another upregulated circRNA in ESCC. It promotes tumor cell proliferation *via*  $\beta$ -catenin signaling, which is positively correlated with poor prognosis[111]. circ-Foxo3 exhibits low expression in ESCC and modulates the miR-23a/PTEN pathway to inhibit ESCC development[112]. circPVT1 has been found to be significantly upregulated in EC and is suggested to play a role in the proliferation of TE-10 tumor cells *via* miR-4663[113].

ciRS-7 is abnormally increased in ESCC and promotes tumor cell growth. It may act as an oncogene, promoting tumor cells proliferation by acting as a miR-876-5p sponge. Meng *et al*[114] have shown that ciRS-7 inhibits autophagy in ESCC induced by starvation or rapamycin immunosuppressive agents. Huang *et al*[115] confirmed that ciRS-7 promotes migration and invasion of ESCC cells *via* miR-7/KLF4 and NF- $\kappa$ B signaling pathways. Knockdown of KLF-4 in ESCC attenuates ciRS-7 invasion[114,115]. Drug resistance in EC is affected by cell proliferation, metastasis, glycolytic enzymes and other factors, among them circRNAs, lncRNAs, miRNAs, and acetyl-coenzyme, a synthetase short-chain family member 2 (ACSS2). Of the above-mentioned factors, lncRNAs have been particularly well studied. For example, ACSS2 affects the absorption of cisplatin in ESCC and protects cancer cells from cisplatin [116]. Conversely, research investigating the relationship between circRNAs and EC drug resistance is lacking. It has been demonstrated that circRNA-001275 upregulates Wnt family member 7A (Wnt7a), which triggers tumor cell growth *via* cisplatin, *via* miR-370-3p, inducing drug resistance[117]. Although there are few studies on circRNA in esophageal cancer drug resistance (Table 4), it can be expected that more circRNAs that play a role in the development and resistance of esophageal cancer will be discovered.

### **circRNAs regulate pancreatic cancer progression and drug resistance**

Pancreatic cancer (PC) has the seventh highest mortality rate among all cancers. It is particularly common in North America, Australia and Europe, and the incidence of PC is higher in males than in females[118]. Several circRNAs have been found to be involved in PC and may be used as therapeutic targets. For example, circBFAR (hsa-circ-0009065) is upregulated in pancreatic ductal adenocarcinoma (PDAC), acting as a miR-34b-5p sponge, and modulates the MET/PI3K/Akt signaling pathway[119]. circFOXK2 is likewise upregulated in PDAC and promotes the expression of ANK1, GDNF and PAX6 by acting as a sponge for miR-942, ultimately promoting the prolifer-

Table 4 circRNAs involved in esophageal cancer gene transcription regulation and drug resistance

Cancer type	circRNA	Gene expression		Mechanism	Drug	Ref.
		Up	Down			
Esophageal cancer	circUBAP2	↑		Acts as miR-422a sponge	NR	[108]
Esophageal cancer	hsa-circ-0006948	↑		miR-490-3p to enhance HMGA2-induced EMT	NR	[109]
Esophageal cancer	circ-0000654	↑		miR-149-5p/IL-6/STAT3 pathway	NR	[110]
Esophageal cancer	circGSK3	↑		β-catenin signal passing	NR	[111]
Esophageal cancer	circ-Foxo3		↓	miR-23a/PTEN pathway	NR	[112]
Esophageal cancer	circPVT1	↑		Acts as miR-4663 sponge	NR	[113]
Esophageal cancer	ciRS-7	↑		Acts as a miR-876-5p sponge	Rapamycin	[114,115]
Esophageal cancer	circRNA-001275	↑		Acts as a miR-370-3p sponge	Cisplatin	[117]

NR: Not reported; circRNA: Circular RNA.

eration of tumor cells. In line with this, knockdown of circFOXK2 was conducive to the inhibition of tumor progression[120]. circ-ADAM9 is highly expressed in PC. It activates the ERK/VEGF signaling pathway *via* miR-217[121]. circ-ASH2L is also highly expressed in PDAC and acts as a sponge for miR-34a, promoting tumor cell proliferation and tumor progression *via* regulation of *Notch1* in PDAC[122]. circ-LDLRAD3 is also overexpressed in PC and regulates cell proliferation *via* the miR-137-3p/PTN axis. It affects prognosis of PC and its knockdown inhibits the invasion of tumor cells[123]. circ-0000977 is upregulated in PC and acts as an miR-153 sponge. Knockdown of circ-0000977 conveys the limiting effect of HIF1A and ADAM10 on PC cells under hypoxia[124]. hsa-circRNA-0007334 is upregulated in PDAC and competes for binding with hsa-miR-144-3p[125]. Similarly as in EC, high expression of ciRS-7 promotes PDAC development *via* acting as an miR-7 sponge and regulating the EGFR/STAT3 signaling pathway. Knockdown of ciRS-7 inhibits the proliferation and invasion of tumor cells[126]. circ-0030235 is upregulated in PDAC and acts as a sponge for miR-1253 and miR-1294. Its expression is a poor prognostic indicator in PDAC [127]. circZMYM2 is also upregulated in PC. It acts as a miR-335-5p sponge and regulates the downstream oncogene *JMJD2C*. Knockdown of circZMYM2 is conducive for the inhibition of tumor growth[128]. circ-0007534 is upregulated in PDAC and acts as a sponge for miR-625 and miR-892b, increasing the proliferation and invasion of tumor cells[129]. circ-IARS is upregulated in PDAC, absorbs miR-122 as a sponge, and increases RhoA activity and F-actin expression, reduces *ZO-1* expression, and promotes tumors by enhancing endothelial cell monolayer permeability, invasion and metastasis[130]. Moreover, circ-PDE8A is upregulated in PDAC and acts as a sponge for miR-338, regulating *MACC1* expression and promoting the growth of tumor cells *via* the *MACC/MET/ERK* or *AKT* signaling pathways[131].

Gemcitabine is an important drug for the treatment of advanced PC. A study showed 68 upregulated and 58 downregulated circRNAs in gemcitabine-treated PANC-1 cells of which two were significantly upregulated (chr14: 10140210 191014644448+, chr4: 52729603-52780244+)[132]. circHIPK3 is highly expressed in PC and promotes gemcitabine resistance in PC cells by acting as a miR-330-5p sponge and targeting *RASSF1*[133].

Overall, circRNAs carry out important roles in tumors. Following further studies, they are expected to serve as new therapeutic targets and biomarkers for tumor diagnosis in the future[134] (Table 5).

## circRNAs PARTICIPATE IN DRUG RESISTANCE

Following chemotherapy, cancers may relapse, and many patients gradually develop resistance to several anticancer drugs. In the present study, we have summarized findings that report that circRNAs may inhibit or promote tumor growth and migration by acting as miR sponges or other pathways *in vitro* and *in vivo*. circRNAs may play the role of vectors in drug resistance due to their unique structure, promoting an inhibitory effect of drugs on tumor cells. Drug resistance of tumor cells

**Table 5 circRNAs involved in pancreatic cancer gene transcription regulation and drug resistance**

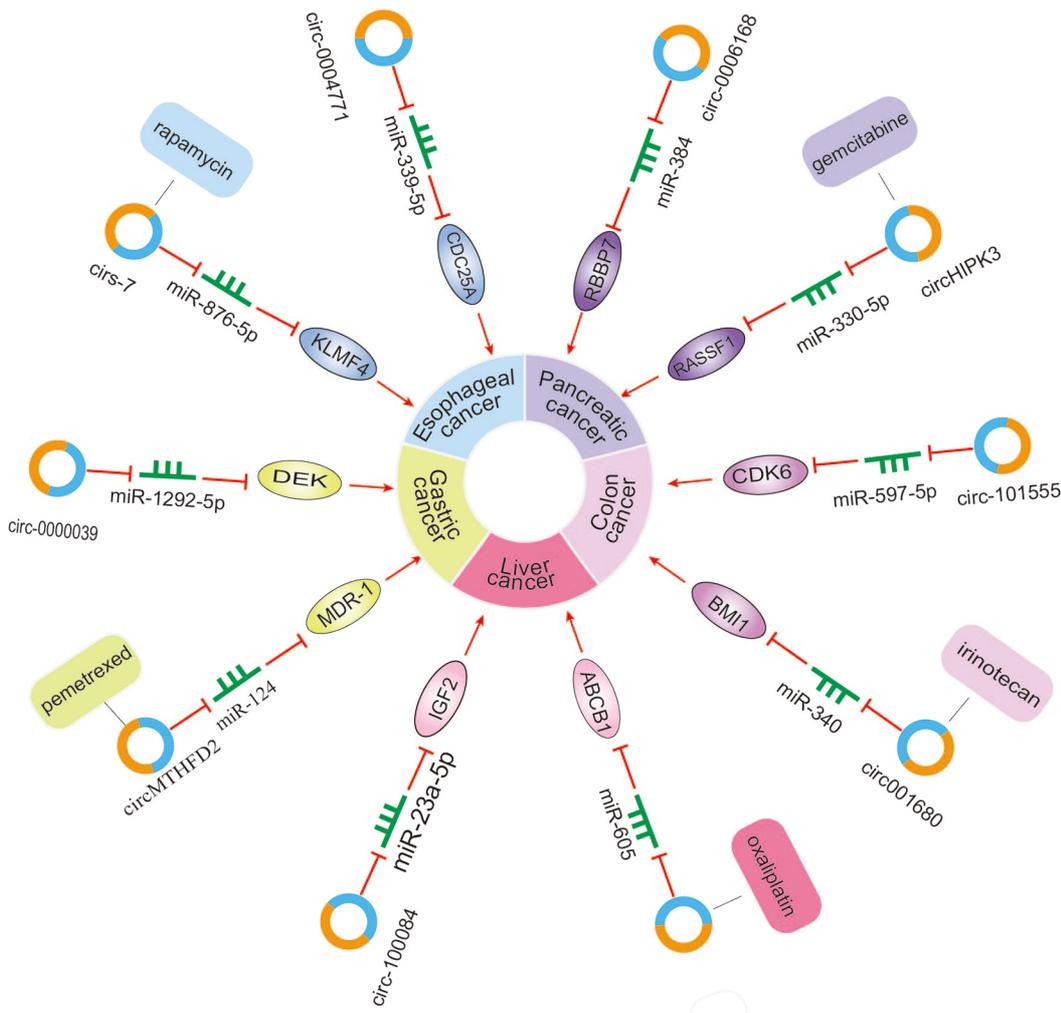
Cancer type	circRNA	Gene expression		Mechanism	Drug	Ref.
		Up	Down			
Pancreatic cancer	circBFAR	↑		Acts as a miR-34b-5p sponge	NR	[119]
Pancreatic cancer	circFOXK2	↑		Acts as miR-942 sponge	NR	[120]
Pancreatic cancer	circ-ADAM9	↑		Activate ERK/VEGF signaling pathway through miR-217	NR	[121]
Pancreatic cancer	circ-ASH2L	↑		Acts as a sponge for miR-34a	NR	[122]
Pancreatic cancer	circ-LDLRAD3	↑		Adjustable <i>via</i> miR-137-3p/PTN axis	NR	[123]
Pancreatic cancer	circ-0000977	↑		Acts as a sponge for miR-153	NR	[124]
Pancreatic cancer	hsa-circRNA-0007334	↑		Competitive binding through hsa-miR-144-3p	NR	[125]
pancreatic cancer	ciRS-7	↑		Acts as miR-7 sponge	NR	[126]
Pancreatic cancer	circ-0030235	↑		Acts as miR-1253 and miR-1294 sponge	NR	[127]
Pancreatic cancer	circZMYM2	↑		Acts as a miR-335-5p sponge	NR	[128]
Pancreatic cancer	circ-0007534	↑		Acts as miR-625, miR-892b sponge	NR	[129]
Pancreatic cancer	circ-IARS	↑		Acts as miR-122 sponge	NR	[130]
Pancreatic cancer	circ-PDE8A	↑		As a sponge of miR-338 to regulate MACC1	NR	[131]
Pancreatic cancer	circHIPK3	↑		Acts as a miR-330-5p sponge	Gemcitabine	[133]

NR: Not reported; circRNA: Circular RNA.

is associated with many factors and the underlying mechanisms are complex. Resistance mechanisms conveyed by circRNAs may be related to glycolysis, ATP levels, or other factors. With regard to the preliminary results of studies on drug resistance, several mechanisms and pathways have been reported to be involved in the regulation of drug resistance by circRNAs in esophageal, pancreatic, colon, liver and gastric cancer. Although further exploring the mechanisms may enable the development of preventive mechanisms against drug resistance among cancer cells, there is still a long way to go for understanding circRNAs and tumor drug resistance (Figure 3).

## CONCLUSION

There is currently a lack of monitoring methods and treatment tools for the development of gastrointestinal tumors and the occurrence of drug resistance. The pathogenesis of gastrointestinal tumors is diverse, including many unstable factors such as DNA damage repair, genome instability and mutations, gene transcription regulation, chromosome modifications, inflammation, tobacco and alcohol, obesity, and autoimmunity. circRNAs exert rich biological functions and play an important role in gastrointestinal tumors. This article discusses the mechanisms of tumor development and drug resistance of gastrointestinal tumors related to circRNAs. While the exact mechanisms of involvement of circRNAs have not been fully elucidated, their important roles in various tumors as observed in initial studies have attracted a lot of attention and have huge potential for future clinical approaches. With advances in biotechnology, new applications such as genetic testing, polymerase chain reaction, high-throughput sequencing, and in-depth research in gastrointestinal tumors, it is expected that circRNAs could be developed into diagnostics or therapeutic targets for the treatment of gastrointestinal tumors. In case circRNAs can become a mass-produced product due to technological innovation, they could be used for clinical treatment. Noninvasive detection distinguishing malignant and benign tumors may also be enabled *via* biotechnological advances. Other options could include the development of new prognosis indicators for patients and monitoring of drug sensitivity, all aimed to ultimately extend patient life and disease-free survival. Based on the presented literature, there is hope that circRNAs may become an effective therapeutic target for cancer treatment in the future.



**Figure 3** Circular RNAs have a regulatory effect on gastrointestinal tumors via signaling molecules, and have been shown to influence drug resistance in gastric, liver, intestinal, esophageal, and pancreatic cancer.

## REFERENCES

- 1 **Maia FCP**, Silva TA, Generoso SV, Correia MITD. Malnutrition is associated with poor health-related quality of life in surgical patients with gastrointestinal cancer. *Nutrition* 2020; **75-76**: 110769 [PMID: 32272362 DOI: 10.1016/j.nut.2020.110769]
- 2 **Varughese LA**, Lau-Min KS, Cambareri C, Damjanov N, Massa R, Reddy N, Oyer R, Teitelbaum U, Tuteja S. DPYD and UGT1A1 Pharmacogenetic Testing in Patients with Gastrointestinal Malignancies: An Overview of the Evidence and Considerations for Clinical Implementation. *Pharmacotherapy* 2020; **40**: 1108-1129 [PMID: 32985005 DOI: 10.1002/phar.2463]
- 3 **Nie H**, Wang Y, Liao Z, Zhou J, Ou C. The function and mechanism of circular RNAs in gastrointestinal tumours. *Cell Prolif* 2020; **53**: e12815 [PMID: 32515024 DOI: 10.1111/cpr.12815]
- 4 **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 U S A* 1976; **73**: 3852-3856 [PMID: 1069269 DOI: 10.1073/pnas.73.11.3852]
- 5 **Cocquerelle C**, Mascrez B, Hétiuin D, Bailleul B. Mis-splicing yields circular RNA molecules. *FASEB J* 1993; **7**: 155-160 [PMID: 7678559 DOI: 10.1096/fasebj.7.1.7678559]
- 6 **Capel B**, Swain A, Nicolis S, Hacker A, Walter M, Koopman P, Goodfellow P, Lovell-Badge R. Circular transcripts of the testis-determining gene Sry in adult mouse testis. *Cell* 1993; **73**: 1019-1030 [PMID: 7684656 DOI: 10.1016/0092-8674(93)90279-y]
- 7 **Salzman J**, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One* 2012; **7**: e30733 [PMID: 22319583 DOI: 10.1371/journal.pone.0030733]
- 8 **Memczak S**, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 2013; **495**: 333-338 [PMID: 23446348 DOI: 10.1038/nature11928]
- 9 **Conn SJ**, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW,

- Gregory PA, Goodall GJ. The RNA binding protein quaking regulates formation of circRNAs. *Cell* 2015; **160**: 1125-1134 [PMID: 25768908 DOI: 10.1016/j.cell.2015.02.014]
- 10 **Pamudurti NR**, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, Hanan M, Wyler E, Perez-Hernandez D, Ramberger E, Shenzen S, Samson M, Dittmar G, Landthaler M, Chekulaeva M, Rajewsky N, Kadener S. Translation of CircRNAs. *Mol Cell* 2017; **66**: 9-21.e7 [PMID: 28344080 DOI: 10.1016/j.molcel.2017.02.021]
  - 11 **Wu X**, Xiao Y, Ma J, Wang A. Circular RNA: A novel potential biomarker for skin diseases. *Pharmacol Res* 2020; **158**: 104841 [PMID: 32404296 DOI: 10.1016/j.phrs.2020.104841]
  - 12 **Li B**, Li Y, Hu L, Liu Y, Zhou Q, Wang M, An Y, Li P. Role of Circular RNAs in the Pathogenesis of Cardiovascular Disease. *J Cardiovasc Transl Res* 2020; **13**: 572-583 [PMID: 32399680 DOI: 10.1007/s12265-019-09912-2]
  - 13 **Yu G**, Yang Z, Peng T, Lv Y. Circular RNAs: Rising stars in lipid metabolism and lipid disorders. *J Cell Physiol* 2021; **236**: 4797-4806 [PMID: 33275299 DOI: 10.1002/jcp.30200]
  - 14 **Yang Y**, Gao X, Zhang M, Yan S, Sun C, Xiao F, Huang N, Yang X, Zhao K, Zhou H, Huang S, Xie B, Zhang N. Novel Role of FBXW7 Circular RNA in Repressing Glioma Tumorigenesis. *J Natl Cancer Inst* 2018; **110** [PMID: 28903484 DOI: 10.1093/jnci/djx166]
  - 15 **Prats AC**, David F, Diallo LH, Roussel E, Tatin F, Garmy-Susini B, Lacazette E. Circular RNA, the Key for Translation. *Int J Mol Sci* 2020; **21** [PMID: 33202605 DOI: 10.3390/ijms21228591]
  - 16 **Zhang L**, Hou C, Chen C, Guo Y, Yuan W, Yin D, Liu J, Sun Z. The role of N<sup>6</sup>-methyladenosine (m<sup>6</sup>A) modification in the regulation of circRNAs. *Mol Cancer* 2020; **19**: 105 [PMID: 32522202 DOI: 10.1186/s12943-020-01224-3]
  - 17 **Nakamoto K**, Abe N, Tsuji G, Kimura Y, Tomoike F, Shimizu Y, Abe H. Chemically synthesized circular RNAs with phosphoramidate linkages enable rolling circle translation. *Chem Commun (Camb)* 2020; **56**: 6217-6220 [PMID: 32369063 DOI: 10.1039/d0cc02140g]
  - 18 **Shan C**, Zhang Y, Hao X, Gao J, Chen X, Wang K. Biogenesis, functions and clinical significance of circRNAs in gastric cancer. *Mol Cancer* 2019; **18**: 136 [PMID: 31519189 DOI: 10.1186/s12943-019-1069-0]
  - 19 **Huang C**, Shan G. What happens at or after transcription: Insights into circRNA biogenesis and function. *Transcription* 2015; **6**: 61-64 [PMID: 26177684 DOI: 10.1080/21541264.2015.1071301]
  - 20 **Di Timoteo G**, Dattilo D, Centrón-Broco A, Colantoni A, Guarnacci M, Rossi F, Incarnato D, Oliviero S, Fatica A, Morlando M, Bozzoni I. Modulation of circRNA Metabolism by m<sup>6</sup>A Modification. *Cell Rep* 2020; **31**: 107641 [PMID: 32402287 DOI: 10.1016/j.celrep.2020.107641]
  - 21 **Zhou WY**, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. *Mol Cancer* 2020; **19**: 172 [PMID: 33317550 DOI: 10.1186/s12943-020-01286-3]
  - 22 **Chen LL**. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol* 2020; **21**: 475-490 [PMID: 32366901 DOI: 10.1038/s41580-020-0243-y]
  - 23 **Qu S**, Zhong Y, Shang R, Zhang X, Song W, Kjems J, Li H. The emerging landscape of circular RNA in life processes. *RNA Biol* 2017; **14**: 992-999 [PMID: 27617908 DOI: 10.1080/15476286.2016.1220473]
  - 24 **Bai Y**, Zhang Y, Han B, Yang L, Chen X, Huang R, Wu F, Chao J, Liu P, Hu G, Zhang JH, Yao H. Circular RNA DLGAP4 Ameliorates Ischemic Stroke Outcomes by Targeting miR-143 to Regulate Endothelial-Mesenchymal Transition Associated with Blood-Brain Barrier Integrity. *J Neurosci* 2018; **38**: 32-50 [PMID: 29114076 DOI: 10.1523/JNEUROSCI.1348-17.2017]
  - 25 **Wang S**, Tang D, Wang W, Yang Y, Wu X, Wang L, Wang D. circLMTK2 acts as a sponge of miR-150-5p and promotes proliferation and metastasis in gastric cancer. *Mol Cancer* 2019; **18**: 162 [PMID: 31722712 DOI: 10.1186/s12943-019-1081-4]
  - 26 **Cervera-Carles L**, Dols-Icardo O, Molina-Porcel L, Alcolea D, Cervantes-Gonzalez A, Muñoz-Llahuna L, Clarimon J. Assessing circular RNAs in Alzheimer's disease and frontotemporal lobar degeneration. *Neurobiol Aging* 2020; **92**: 7-11 [PMID: 32335360 DOI: 10.1016/j.neurobiolaging.2020.03.017]
  - 27 **Hansen TB**, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. *Nature* 2013; **495**: 384-388 [PMID: 23446346 DOI: 10.1038/nature11993]
  - 28 **Qu X**, Li Z, Chen J, Hou L. The emerging roles of circular RNAs in CNS injuries. *J Neurosci Res* 2020; **98**: 1485-1497 [PMID: 32052488 DOI: 10.1002/jnr.24591]
  - 29 **He J**, Xie Q, Xu H, Li J, Li Y. Circular RNAs and cancer. *Cancer Lett* 2017; **396**: 138-144 [PMID: 28342987 DOI: 10.1016/j.canlet.2017.03.027]
  - 30 **Holdt LM**, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, Kohlmaier A, Herbst A, Northoff BH, Nicolaou A, Gäbel G, Beutner F, Scholz M, Thiery J, Musunuru K, Krohn K, Mann M, Teupser D. Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. *Nat Commun* 2016; **7**: 12429 [PMID: 27539542 DOI: 10.1038/ncomms12429]
  - 31 **Chen J**, Li Y, Zheng Q, Bao C, He J, Chen B, Lyu D, Zheng B, Xu Y, Long Z, Zhou Y, Zhu H, Wang Y, He X, Shi Y, Huang S. Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. *Cancer Lett* 2017; **388**: 208-219 [PMID: 27986464 DOI: 10.1016/j.canlet.2016.12.006]
  - 32 **Li R**, Jiang J, Shi H, Qian H, Zhang X, Xu W. CircRNA: a rising star in gastric cancer. *Cell Mol Life Sci* 2020; **77**: 1661-1680 [PMID: 31659415 DOI: 10.1007/s00018-019-03345-5]

- 33 **Petkovic S**, Müller S. RNA circularization strategies in vivo and in vitro. *Nucleic Acids Res* 2015; **43**: 2454-2465 [PMID: 25662225 DOI: 10.1093/nar/gkv045]
- 34 **Villaseñor R**, Baubec T. Regulatory mechanisms governing chromatin organization and function. *Curr Opin Cell Biol* 2021; **70**: 10-17 [PMID: 33276273 DOI: 10.1016/j.ceb.2020.10.015]
- 35 **Kim Y**, Yu H. Shaping of the 3D genome by the ATPase machine cohesin. *Exp Mol Med* 2020; **52**: 1891-1897 [PMID: 33268833 DOI: 10.1038/s12276-020-00526-2]
- 36 **Tang Z**, Li X, Zhao J, Qian F, Feng C, Li Y, Zhang J, Jiang Y, Yang Y, Wang Q, Li C. TRCirc: a resource for transcriptional regulation information of circRNAs. *Brief Bioinform* 2019; **20**: 2327-2333 [PMID: 30184150 DOI: 10.1093/bib/bby083]
- 37 **Tan S**, Kang Y, Li H, He HQ, Zheng L, Wu SQ, Ai K, Zhang L, Xu R, Zhang XZ, Zhao XK, Zhu X. circST6GALNAC6 suppresses bladder cancer metastasis by sponging miR-200a-3p to modulate the STMN1/EMT axis. *Cell Death Dis* 2021; **12**: 168 [PMID: 33568625 DOI: 10.1038/s41419-021-03459-4]
- 38 **Lacerda R**, Menezes J, Romão L. More than just scanning: the importance of cap-independent mRNA translation initiation for cellular stress response and cancer. *Cell Mol Life Sci* 2017; **74**: 1659-1680 [PMID: 27913822 DOI: 10.1007/s00018-016-2428-2]
- 39 **Dong R**, Ma XK, Chen LL, Yang L. Increased complexity of circRNA expression during species evolution. *RNA Biol* 2017; **14**: 1064-1074 [PMID: 27982734 DOI: 10.1080/15476286.2016.1269999]
- 40 **Hu X**, Zhu M, Zhang X, Liu B, Liang Z, Huang L, Xu J, Yu L, Li K, Zar MS, Xue R, Cao G, Gong C. Identification and characterization of circular RNAs in the silkworm midgut following Bombyx mori cytoplasmic polyhedrosis virus infection. *RNA Biol* 2018; **15**: 292-301 [PMID: 29268657 DOI: 10.1080/15476286.2017.1411461]
- 41 **Granados-Riveron JT**, Aquino-Jarquín G. The complexity of the translation ability of circRNAs. *Biochim Biophys Acta* 2016; **1859**: 1245-1251 [PMID: 27449861 DOI: 10.1016/j.bbagr.2016.07.009]
- 42 **Starke S**, Jost I, Rossbach O, Schneider T, Schreiner S, Hung LH, Bindereif A. Exon circularization requires canonical splice signals. *Cell Rep* 2015; **10**: 103-111 [PMID: 25543144 DOI: 10.1016/j.celrep.2014.12.002]
- 43 **Li Z**, Huang C, Bao C, Chen L, Lin M, Wang X, Zhong G, Yu B, Hu W, Dai L, Zhu P, Chang Z, Wu Q, Zhao Y, Jia Y, Xu P, Liu H, Shan G. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol* 2015; **22**: 256-264 [PMID: 25664725 DOI: 10.1038/nsmb.2959]
- 44 **Lei M**, Zheng G, Ning Q, Zheng J, Dong D. Translation and functional roles of circular RNAs in human cancer. *Mol Cancer* 2020; **19**: 30 [PMID: 32059672 DOI: 10.1186/s12943-020-1135-7]
- 45 **Tang Q**, Hann SS. Biological Roles and Mechanisms of Circular RNA in Human Cancers. *Oncol Targets Ther* 2020; **13**: 2067-2092 [PMID: 32210574 DOI: 10.2147/OTT.S233672]
- 46 **Li X**, Wang J, Zhang C, Lin C, Zhang J, Zhang W, Lu Y, Zheng L, Li X. Circular RNA circITGA7 inhibits colorectal cancer growth and metastasis by modulating the Ras pathway and upregulating transcription of its host gene ITGA7. *J Pathol* 2018; **246**: 166-179 [PMID: 29943828 DOI: 10.1002/path.5125]
- 47 **Xie M**, Yu T, Jing X, Ma L, Fan Y, Yang F, Ma P, Jiang H, Wu X, Shu Y, Xu T. Exosomal circSHKBP1 promotes gastric cancer progression via regulating the miR-582-3p/HUR/VEGF axis and suppressing HSP90 degradation. *Mol Cancer* 2020; **19**: 112 [PMID: 32600329 DOI: 10.1186/s12943-020-01208-3]
- 48 **Bannister AJ**, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res* 2011; **21**: 381-395 [PMID: 21321607 DOI: 10.1038/cr.2011.22]
- 49 **Tang L**, Xiong W, Zhang L, Wang D, Wang Y, Wu Y, Wei F, Mo Y, Hou X, Shi L, Xiong F, Zhang S, Gong Z, Liao Q, Xiang B, Zhang W, Zhou M, Li X, Li G, Guo C, Zeng Z. circSETD3 regulates MAPRE1 through miR-615-5p and miR-1538 sponges to promote migration and invasion in nasopharyngeal carcinoma. *Oncogene* 2021; **40**: 307-321 [PMID: 33122825 DOI: 10.1038/s41388-020-01531-5]
- 50 **Jie M**, Wu Y, Gao M, Li X, Liu C, Ouyang Q, Tang Q, Shan C, Lv Y, Zhang K, Dai Q, Chen Y, Zeng S, Li C, Wang L, He F, Hu C, Yang S. CircMRPS35 suppresses gastric cancer progression via recruiting KAT7 to govern histone modification. *Mol Cancer* 2020; **19**: 56 [PMID: 32164722 DOI: 10.1186/s12943-020-01160-2]
- 51 **He Y**, Zhang Q, Zheng Q, Yu X, Guo W. Distinct 5-methylcytosine profiles of circular RNA in human hepatocellular carcinoma. *Am J Transl Res* 2020; **12**: 5719-5729 [PMID: 33042451]
- 52 **Zhao Z**, Song J, Tang B, Fang S, Zhang D, Zheng L, Wu F, Gao Y, Chen C, Hu X, Weng Q, Yang Y, Tu J, Ji J. CircSOD2 induced epigenetic alteration drives hepatocellular carcinoma progression through activating JAK2/STAT3 signaling pathway. *J Exp Clin Cancer Res* 2020; **39**: 259 [PMID: 33234142 DOI: 10.1186/s13046-020-01769-7]
- 53 **Wang Y**, Shi S, Zhang Q, Dong H, Zhang J. MicroRNA-206 upregulation relieves circTCF25-induced osteosarcoma cell proliferation and migration. *J Cell Physiol* 2020 [PMID: 32052450 DOI: 10.1002/jcp.29570]
- 54 **Wang Y**, Xu R, Zhang D, Lu T, Yu W, Wo Y, Liu A, Sui T, Cui J, Qin Y, Dong Y, Leng X, Kong D, Du W, Huang Z, Su W, Yuan T, Sun X, Wang J, Jiao W. Circ-ZKSCAN1 regulates FAM83A expression and inactivates MAPK signaling by targeting miR-330-5p to promote non-small cell lung cancer progression. *Transl Lung Cancer Res* 2019; **8**: 862-875 [PMID: 32010565 DOI: 10.21037/tlcr.2019.11.04]

- 55 **Pan G**, Mao A, Liu J, Lu J, Ding J, Liu W. Circular RNA hsa\_circ\_0061825 (circ-TFF1) contributes to breast cancer progression through targeting miR-326/TFF1 signalling. *Cell Prolif* 2020; **53**: e12720 [PMID: 31961997 DOI: 10.1111/cpr.12720]
- 56 **Li Y**, Li C, Xu R, Wang Y, Li D, Zhang B. A novel circFMN2 promotes tumor proliferation in CRC by regulating the miR-1182/hTERT signaling pathways. *Clin Sci (Lond)* 2019; **133**: 2463-2479 [PMID: 31738400 DOI: 10.1042/CS20190715]
- 57 **Wang GJ**, Yu TY, Li YR, Liu YJ, Deng BB. Circ\_0000190 suppresses gastric cancer progression potentially via inhibiting miR-1252/PAK3 pathway. *Cancer Cell Int* 2020; **20**: 351 [PMID: 32742198 DOI: 10.1186/s12935-020-01422-5]
- 58 **Kumala S**, Fujarewicz K, Jayaraju D, Rzeszowska-Wolny J, Hancock R. Repair of DNA strand breaks in a minichromosome in vivo: kinetics, modeling, and effects of inhibitors. *PLoS One* 2013; **8**: e52966 [PMID: 23382828 DOI: 10.1371/journal.pone.0052966]
- 59 **Gamper AM**, Rofougaran R, Watkins SC, Greenberger JS, Beumer JH, Bakkenist CJ. ATR kinase activation in G1 phase facilitates the repair of ionizing radiation-induced DNA damage. *Nucleic Acids Res* 2013; **41**: 10334-10344 [PMID: 24038466 DOI: 10.1093/nar/gkt833]
- 60 **Podraska M**, Ciesielska S, Kluiver J, van den Berg A, Dzikiewicz-Krawczyk A, Slezak-Prochazka I. Non-Coding RNAs in Cancer Radiosensitivity: MicroRNAs and lncRNAs as Regulators of Radiation-Induced Signaling Pathways. *Cancers (Basel)* 2020; **12** [PMID: 32585857 DOI: 10.3390/cancers12061662]
- 61 **Xu X**, Zhang J, Tian Y, Gao Y, Dong X, Chen W, Yuan X, Yin W, Xu J, Chen K, He C, Wei L. CircRNA inhibits DNA damage repair by interacting with host gene. *Mol Cancer* 2020; **19**: 128 [PMID: 32838810 DOI: 10.1186/s12943-020-01246-x]
- 62 **Jonaitis P**, Kiudelis V, Streleckiene G, Gedgaudas R, Skieceviciene J, Kupcinskas J. Novel Biomarkers in the Diagnosis of Benign and Malignant GI Diseases. *Dig Dis* 2021 [PMID: 33647906 DOI: 10.1159/000515522]
- 63 **Xu T**, Wang M, Jiang L, Ma L, Wan L, Chen Q, Wei C, Wang Z. CircRNAs in anticancer drug resistance: recent advances and future potential. *Mol Cancer* 2020; **19**: 127 [PMID: 32799866 DOI: 10.1186/s12943-020-01240-3]
- 64 **Wei L**, Sun J, Zhang N, Zheng Y, Wang X, Lv L, Liu J, Xu Y, Shen Y, Yang M. Noncoding RNAs in gastric cancer: implications for drug resistance. *Mol Cancer* 2020; **19**: 62 [PMID: 32192494 DOI: 10.1186/s12943-020-01185-7]
- 65 **Yuan X**, Yuan Y, He Z, Li D, Zeng B, Ni Q, Yang M, Yang D. The Regulatory Functions of Circular RNAs in Digestive System Cancers. *Cancers (Basel)* 2020; **12** [PMID: 32213977 DOI: 10.3390/cancers12030770]
- 66 **Lin X**, Huang C, Chen Z, Wang H, Zeng Y. CircRNA\_100876 Is Upregulated in Gastric Cancer (GC) and Promotes the GC Cells' Growth, Migration and Invasion via miR-665/YAP1 Signaling. *Front Genet* 2020; **11**: 546275 [PMID: 33262782 DOI: 10.3389/fgene.2020.546275]
- 67 **Pu Z**, Xu M, Yuan X, Xie H, Zhao J. Circular RNA circCUL3 Accelerates the Warburg Effect Progression of Gastric Cancer through Regulating the STAT3/HK2 Axis. *Mol Ther Nucleic Acids* 2020; **22**: 310-318 [PMID: 33230436 DOI: 10.1016/j.omtn.2020.08.023]
- 68 **Wang H**, Sun G, Xu P, Lv J, Zhang X, Zhang L, Wang S, Cao J, Xia Y, Xuan Z, Li B, Huang X, Jiang T, Fang L, Xu Z. Circular RNA TMEM87A promotes cell proliferation and metastasis of gastric cancer by elevating ULK1 via sponging miR-142-5p. *J Gastroenterol* 2021; **56**: 125-138 [PMID: 33155080 DOI: 10.1007/s00535-020-01744-1]
- 69 **Fang J**, Chen W, Meng X. Downregulating circRNA\_0044516 Inhibits Cell Proliferation in Gastric Cancer Through miR-149/Wnt1/ $\beta$ -catenin Pathway. *J Gastrointest Surg* 2021; **25**: 1696-1705 [PMID: 33140323 DOI: 10.1007/s11605-020-04834-w]
- 70 **Fan D**, Wang C, Wang D, Zhang N, Yi T. Circular RNA circ\_0000039 enhances gastric cancer progression through miR-1292-5p/DEK axis. *Cancer Biomark* 2021; **30**: 167-177 [PMID: 33104023 DOI: 10.3233/CBM-201754]
- 71 **Ma C**, Wang X, Yang F, Zang Y, Liu J, Xu X, Li W, Jia J, Liu Z. Circular RNA hsa\_circ\_0004872 inhibits gastric cancer progression via the miR-224/Smad4/ADAR1 successive regulatory circuit. *Mol Cancer* 2020; **19**: 157 [PMID: 33172486 DOI: 10.1186/s12943-020-01268-5]
- 72 **Peng Y**, Wang HH. Cir-ITCH inhibits gastric cancer migration, invasion and proliferation by regulating the Wnt/ $\beta$ -catenin pathway. *Sci Rep* 2020; **10**: 17443 [PMID: 33060778 DOI: 10.1038/s41598-020-74452-8]
- 73 **Xia T**, Pan Z, Zhang J. CircPDZD8 promotes gastric cancer progression by regulating CHD9 via sponging miR-197-5p. *Aging (Albany NY)* 2020; **12**: 19352-19364 [PMID: 33049714 DOI: 10.18632/aging.103805]
- 74 **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**: 10290-10299 [PMID: 31841184 DOI: 10.26355/eurrev\_201912\_19667]
- 75 **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** [PMID: 31793989 DOI: 10.1042/BSR20193045]
- 76 **Huang X**, Li Z, Zhang Q, Wang W, Li B, Wang L, Xu Z, Zeng A, Zhang X, He Z, Li Q, Sun G, Wang S, Zhang L, Xu H. Circular RNA AKT3 upregulates PIK3R1 to enhance cisplatin resistance in gastric cancer via miR-198 suppression. *Mol Cancer* 2019; **18**: 71 [PMID: 30927924 DOI: 10.1186/s12943-019-0969-3]

- 77 **Huang XX**, Zhang Q, Hu H, Jin Y, Zeng AL, Xia YB, Xu L. A novel circular RNA circFN1 enhances cisplatin resistance in gastric cancer via sponging miR-182-5p. *J Cell Biochem* 2020 [PMID: 31898357 DOI: 10.1002/jcb.29641]
- 78 **Hu J**, Li P, Song Y, Ge YX, Meng XM, Huang C, Li J, Xu T. Progress and prospects of circular RNAs in Hepatocellular carcinoma: Novel insights into their function. *J Cell Physiol* 2018; **233**: 4408-4422 [PMID: 28833094 DOI: 10.1002/jcp.26154]
- 79 **Cheng F**, Wang L, Zhang J. Circular RNA 0016788 displays as a biomarker for tumor progression and poor prognosis in surgical hepatocellular carcinoma patients. *J Clin Lab Anal* 2020; **34**: e23300 [PMID: 32319701 DOI: 10.1002/jcla.23300]
- 80 **Yao Z**, Luo J, Hu K, Lin J, Huang H, Wang Q, Zhang P, Xiong Z, He C, Huang Z, Liu B, Yang Y. ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. *Mol Oncol* 2017; **11**: 422-437 [PMID: 28211215 DOI: 10.1002/1878-0261.12045]
- 81 **Yang J**, Li Y, Yu Z, Zhou Y, Tu J, Lou J, Wang Y. Circular RNA Circ100084 functions as sponge of miR23a5p to regulate IGF2 expression in hepatocellular carcinoma. *Mol Med Rep* 2020; **21**: 2395-2404 [PMID: 32323783 DOI: 10.3892/mmr.2020.11069]
- 82 **Chen W**, Quan Y, Fan S, Wang H, Liang J, Huang L, Chen L, Liu Q, He P, Ye Y. Exosome-transmitted circular RNA hsa\_circ\_0051443 suppresses hepatocellular carcinoma progression. *Cancer Lett* 2020; **475**: 119-128 [PMID: 32014458 DOI: 10.1016/j.canlet.2020.01.022]
- 83 **Fu Y**, Cai L, Lei X, Wang D. Circular RNA ABCB10 promotes hepatocellular carcinoma progression by increasing HMG20A expression by sponging miR-670-3p. *Cancer Cell Int* 2019; **19**: 338 [PMID: 31889891 DOI: 10.1186/s12935-019-1055-z]
- 84 **Zhou S**, Wei J, Wang Y, Liu X. Cisplatin resistance-associated circRNA\_101237 serves as a prognostic biomarker in hepatocellular carcinoma. *Exp Ther Med* 2020; **19**: 2733-2740 [PMID: 32226487 DOI: 10.3892/etm.2020.8526]
- 85 **Wu MY**, Tang YP, Liu JJ, Liang R, Luo XL. Global transcriptomic study of circRNAs expression profile in sorafenib resistant hepatocellular carcinoma cells. *J Cancer* 2020; **11**: 2993-3001 [PMID: 32226514 DOI: 10.7150/jca.39854]
- 86 **Chen H**, Liu S, Li M, Huang P, Li X. circ\_0003418 Inhibits Tumorigenesis And Cisplatin Chemoresistance Through Wnt/ $\beta$ -Catenin Pathway In Hepatocellular Carcinoma. *Onco Targets Ther* 2019; **12**: 9539-9549 [PMID: 31807029 DOI: 10.2147/OTT.S229507]
- 87 **Li J**, Qin X, Wu R, Wan L, Zhang L, Liu R. Circular RNA circFBXO11 modulates hepatocellular carcinoma progress and oxaliplatin resistance through miR-605/FOXO3/ABCB1 axis. *J Cell Mol Med* 2020; **24**: 5152-5161 [PMID: 32222024 DOI: 10.1111/jcmm.15162]
- 88 **Sun P**, Fan X, Hu X, Fu X, Wei Q, Zang Y. circPCNX and Pecanex Promote Hepatocellular Carcinoma Cell Viability by Inhibiting miR-506. *Cancer Manag Res* 2019; **11**: 10957-10967 [PMID: 32099459 DOI: 10.2147/CMAR.S232940]
- 89 **Rawla P**, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 2019; **14**: 89-103 [PMID: 31616522 DOI: 10.5114/pg.2018.81072]
- 90 **Karimzadeh MR**, Zarin M, Ehtesham N, Khosravi S, Soosanabadi M, Mosallaei M, Pourdavoud P. MicroRNA binding site polymorphism in inflammatory genes associated with colorectal cancer: literature review and bioinformatics analysis. *Cancer Gene Ther* 2020; **27**: 739-753 [PMID: 32203060 DOI: 10.1038/s41417-020-0172-0]
- 91 **Chen RX**, Chen X, Xia LP, Zhang JX, Pan ZZ, Ma XD, Han K, Chen JW, Judde JG, Deas O, Wang F, Ma NF, Guan X, Yun JP, Wang FW, Xu RH, Dan Xie. N<sup>6</sup>-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis. *Nat Commun* 2019; **10**: 4695 [PMID: 31619685 DOI: 10.1038/s41467-019-12651-2]
- 92 **Chen Z**, Ren R, Wan D, Wang Y, Xue X, Jiang M, Shen J, Han Y, Liu F, Shi J, Kuang Y, Li W, Zhi Q. Hsa\_circ\_101555 functions as a competing endogenous RNA of miR-597-5p to promote colorectal cancer progression. *Oncogene* 2019; **38**: 6017-6034 [PMID: 31300733 DOI: 10.1038/s41388-019-0857-8]
- 93 **Zeng K**, Chen X, Xu M, Liu X, Hu X, Xu T, Sun H, Pan Y, He B, Wang S. CircHIPK3 promotes colorectal cancer growth and metastasis by sponging miR-7. *Cell Death Dis* 2018; **9**: 417 [PMID: 29549306 DOI: 10.1038/s41419-018-0454-8]
- 94 **Hsiao KY**, Lin YC, Gupta SK, Chang N, Yen L, Sun HS, Tsai SJ. Noncoding Effects of Circular RNA CCDC66 Promote Colon Cancer Growth and Metastasis. *Cancer Res* 2017; **77**: 2339-2350 [PMID: 28249903 DOI: 10.1158/0008-5472.CAN-16-1883]
- 95 **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** [PMID: 32187976 DOI: 10.3390/cancers12030697]
- 96 **Guo JN**, Li J, Zhu CL, Feng WT, Shao JX, Wan L, Huang MD, He JD. Comprehensive profile of differentially expressed circular RNAs reveals that hsa\_circ\_0000069 is upregulated and promotes cell proliferation, migration, and invasion in colorectal cancer. *Onco Targets Ther* 2016; **9**: 7451-7458 [PMID: 28003761 DOI: 10.2147/OTT.S123220]
- 97 **Fujita K**, Kubota Y, Ishida H, Sasaki Y. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. *World J Gastroenterol* 2015; **21**: 12234-12248 [PMID: 26604633 DOI: 10.3748/wjg.v21.i43.12234]
- 98 **Jian X**, He H, Zhu J, Zhang Q, Zheng Z, Liang X, Chen L, Yang M, Peng K, Zhang Z, Liu T, Ye Y,

- Jiao H, Wang S, Zhou W, Ding Y, Li T. Hsa\_circ\_001680 affects the proliferation and migration of CRC and mediates its chemoresistance by regulating BMI1 through miR-340. *Mol Cancer* 2020; **19**: 20 [PMID: 32005118 DOI: 10.1186/s12943-020-1134-8]
- 99 Wang X, Zhang H, Yang H, Bai M, Ning T, Deng T, Liu R, Fan Q, Zhu K, Li J, Zhan Y, Ying G, Ba Y. Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer. *Mol Oncol* 2020; **14**: 539-555 [PMID: 31901148 DOI: 10.1002/1878-0261.12629]
- 100 Hon KW, Ab-Mutalib NS, Abdullah NMA, Jamal R, Abu N. Extracellular Vesicle-derived circular RNAs confers chemoresistance in Colorectal cancer. *Sci Rep* 2019; **9**: 16497 [PMID: 31712601 DOI: 10.1038/s41598-019-53063-y]
- 101 Abu N, Hon KW, Jeyaraman S, Yahaya A, Abdullah NM, Mustangin M, Sulaiman SA, Jamal R, Ab-Mutalib NS. Identification of differentially expressed circular RNAs in chemoresistant colorectal cancer. *Epigenomics* 2019; **11**: 875-884 [PMID: 31020847 DOI: 10.2217/epi-2019-0042]
- 102 Ehrhart IC, Parker PE, Weidner WJ, Dabney JM, Scott JB, Haddy FJ. Coronary vascular and myocardial responses to carotid body stimulation in the dog. *Am J Physiol* 1975; **229**: 754-760 [PMID: 2017 DOI: 10.1152/ajplegacy.1975.229.3.754]
- 103 Lai M, Liu G, Li R, Bai H, Zhao J, Xiao P, Mei J. Hsa\_circ\_0079662 induces the resistance mechanism of the chemotherapy drug oxaliplatin through the TNF- $\alpha$  pathway in human colon cancer. *J Cell Mol Med* 2020; **24**: 5021-5027 [PMID: 32243061 DOI: 10.1111/jcmm.15122]
- 104 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**: 1743-1754 [PMID: 32141542 DOI: 10.26355/eurrev\_202002\_20351]
- 105 Naeli P, Pourhanifeh MH, Karimzadeh MR, Shabaninejad Z, Movahedpour A, Tarrahimofrad H, Mirzaei HR, Bafrani HH, Savardashtaki A, Mirzaei H, Hamblin MR. Circular RNAs and gastrointestinal cancers: Epigenetic regulators with a prognostic and therapeutic role. *Crit Rev Oncol Hematol* 2020; **145**: 102854 [PMID: 31877535 DOI: 10.1016/j.critrevonc.2019.102854]
- 106 Fan L, Cao Q, Liu J, Zhang J, Li B. Circular RNA profiling and its potential for esophageal squamous cell cancer diagnosis and prognosis. *Mol Cancer* 2019; **18**: 16 [PMID: 30674324 DOI: 10.1186/s12943-018-0936-4]
- 107 Huang E, Fu J, Yu Q, Xie P, Yang Z, Ji H, Wang L, Luo G, Zhang Y, Li K. CircRNA hsa\_circ\_0004771 promotes esophageal squamous cell cancer progression via miR-339-5p/CDC25A axis. *Epigenomics* 2020; **12**: 587-603 [PMID: 32050790 DOI: 10.2217/epi-2019-0404]
- 108 Wu Y, Zhi L, Zhao Y, Yang L, Cai F. Knockdown of circular RNA UBAP2 inhibits the malignant behaviours of esophageal squamous cell carcinoma by microRNA-422a/Rab10 axis. *Clin Exp Pharmacol Physiol* 2020; **47**: 1283-1290 [PMID: 32012318 DOI: 10.1111/1440-1681.13269]
- 109 Pan Z, Lin J, Wu D, He X, Wang W, Hu X, Zhang L, Wang M. Hsa\_circ\_0006948 enhances cancer progression and epithelial-mesenchymal transition through the miR-490-3p/HMG2 axis in esophageal squamous cell carcinoma. *Aging (Albany NY)* 2019; **11**: 11937-11954 [PMID: 31881015 DOI: 10.18632/aging.102519]
- 110 Xu Z, Tie X, Li N, Yi Z, Shen F, Zhang Y. Circular RNA hsa\_circ\_0000654 promotes esophageal squamous cell carcinoma progression by regulating the miR-149-5p/IL-6/STAT3 pathway. *IUBMB Life* 2020; **72**: 426-439 [PMID: 31778020 DOI: 10.1002/iub.2202]
- 111 Hu X, Wu D, He X, Zhao H, He Z, Lin J, Wang K, Wang W, Pan Z, Lin H, Wang M. circGSK3 $\beta$  promotes metastasis in esophageal squamous cell carcinoma by augmenting  $\beta$ -catenin signaling. *Mol Cancer* 2019; **18**: 160 [PMID: 31722716 DOI: 10.1186/s12943-019-1095-y]
- 112 Xing Y, Zha WJ, Li XM, Li H, Gao F, Ye T, Du WQ, Liu YC. Circular RNA circ-Foxo3 inhibits esophageal squamous cell cancer progression via the miR-23a/PTEN axis. *J Cell Biochem* 2020; **121**: 2595-2605 [PMID: 31680314 DOI: 10.1002/jcb.29481]
- 113 Zhong R, Chen Z, Mo T, Li Z, Zhang P. Potential Role of circPVT1 as a proliferative factor and treatment target in esophageal carcinoma. *Cancer Cell Int* 2019; **19**: 267 [PMID: 31636510 DOI: 10.1186/s12935-019-0985-9]
- 114 Meng L, Liu S, Ding P, Chang S, Sang M. Circular RNA ciRS-7 inhibits autophagy of ESCC cells by functioning as miR-1299 sponge to target EGFR signaling. *J Cell Biochem* 2020; **121**: 1039-1049 [PMID: 31490018 DOI: 10.1002/jcb.29339]
- 115 Huang H, Wei L, Qin T, Yang N, Li Z, Xu Z. Circular RNA ciRS-7 triggers the migration and invasion of esophageal squamous cell carcinoma via miR-7/KLF4 and NF- $\kappa$ B signals. *Cancer Biol Ther* 2019; **20**: 73-80 [PMID: 30207835 DOI: 10.1080/15384047.2018.1507254]
- 116 Mi L, Zhou Y, Wu D, Tao Q, Wang X, Zhu H, Gao X, Wang J, Ling R, Deng J, Mao C, Chen D. ACSS2/AMPK/PCNA pathwaydriven proliferation and chemoresistance of esophageal squamous carcinoma cells under nutrient stress. *Mol Med Rep* 2019; **20**: 5286-5296 [PMID: 31638228 DOI: 10.3892/mmr.2019.10735]
- 117 Zou FW, Yang SZ, Li WY, Liu CY, Liu XH, Hu CH, Liu ZH, Xu S. circRNA\_001275 upregulates Wnt7a expression by competitively sponging miR3703p to promote cisplatin resistance in esophageal cancer. *Int J Oncol* 2020; **57**: 151-160 [PMID: 32319613 DOI: 10.3892/ijo.2020.5050]
- 118 Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 2020; **159**: 335-349.e15 [PMID: 32247694 DOI: 10.1053/j.gastro.2020.02.068]
- 119 Guo X, Zhou Q, Su D, Luo Y, Fu Z, Huang L, Li Z, Jiang D, Kong Y, Chen R, Chen C. Circular RNA circBFAR promotes the progression of pancreatic ductal adenocarcinoma via the miR-34b-

- 5p/MET/Akt axis. *Mol Cancer* 2020; **19**: 83 [PMID: 32375768 DOI: 10.1186/s12943-020-01196-4]
- 120 **Wong CH**, Lou UK, Li Y, Chan SL, Tong JH, To KF, Chen Y. CircFOXK2 Promotes Growth and Metastasis of Pancreatic Ductal Adenocarcinoma by Complexing with RNA-Binding Proteins and Sponging MiR-942. *Cancer Res* 2020; **80**: 2138-2149 [PMID: 32217695 DOI: 10.1158/0008-5472.CAN-19-3268]
- 121 **Xing C**, Ye H, Wang W, Sun M, Zhang J, Zhao Z, Jiang G. Circular RNA ADAM9 facilitates the malignant behaviours of pancreatic cancer by sponging miR-217 and upregulating PRSS3 expression. *Artif Cells Nanomed Biotechnol* 2019; **47**: 3920-3928 [PMID: 31810373 DOI: 10.1080/21691401.2019.1671856]
- 122 **Chen Y**, Li Z, Zhang M, Wang B, Ye J, Zhang Y, Tang D, Ma D, Jin W, Li X, Wang S. Circ-ASH2L promotes tumor progression by sponging miR-34a to regulate Notch1 in pancreatic ductal adenocarcinoma. *J Exp Clin Cancer Res* 2019; **38**: 466 [PMID: 31718694 DOI: 10.1186/s13046-019-1436-0]
- 123 **Yao J**, Zhang C, Chen Y, Gao S. Downregulation of circular RNA circ-LDLRAD3 suppresses pancreatic cancer progression through miR-137-3p/PTN axis. *Life Sci* 2019; **239**: 116871 [PMID: 31521692 DOI: 10.1016/j.lfs.2019.116871]
- 124 **Ou ZL**, Luo Z, Wei W, Liang S, Gao TL, Lu YB. Hypoxia-induced shedding of MICA and HIF1A-mediated immune escape of pancreatic cancer cells from NK cells: role of circ\_0000977/miR-153 axis. *RNA Biol* 2019; **16**: 1592-1603 [PMID: 31402756 DOI: 10.1080/15476286.2019.1649585]
- 125 **Yang J**, Cong X, Ren M, Sun H, Liu T, Chen G, Wang Q, Li Z, Yu S, Yang Q. Circular RNA hsa\_circRNA\_0007334 is Predicted to Promote MMP7 and COL1A1 Expression by Functioning as a miRNA Sponge in Pancreatic Ductal Adenocarcinoma. *J Oncol* 2019; **2019**: 7630894 [PMID: 31428151 DOI: 10.1155/2019/7630894]
- 126 **Liu L**, Liu FB, Huang M, Xie K, Xie QS, Liu CH, Shen MJ, Huang Q. Circular RNA ciRS-7 promotes the proliferation and metastasis of pancreatic cancer by regulating miR-7-mediated EGFR/STAT3 signaling pathway. *Hepatobiliary Pancreat Dis Int* 2019; **18**: 580-586 [PMID: 30898507 DOI: 10.1016/j.hbpd.2019.03.003]
- 127 **Xu Y**, Yao Y, Gao P, Cui Y. Upregulated circular RNA circ\_0030235 predicts unfavorable prognosis in pancreatic ductal adenocarcinoma and facilitates cell progression by sponging miR-1253 and miR-1294. *Biochem Biophys Res Commun* 2019; **509**: 138-142 [PMID: 30591218 DOI: 10.1016/j.bbrc.2018.12.088]
- 128 **An Y**, Cai H, Zhang Y, Liu S, Duan Y, Sun D, Chen X, He X. circZMYM2 Competed Endogenously with miR-335-5p to Regulate JMJD2C in Pancreatic Cancer. *Cell Physiol Biochem* 2018; **51**: 2224-2236 [PMID: 30537731 DOI: 10.1159/000495868]
- 129 **Hao L**, Rong W, Bai L, Cui H, Zhang S, Li Y, Chen D, Meng X. Upregulated circular RNA circ\_0007534 indicates an unfavorable prognosis in pancreatic ductal adenocarcinoma and regulates cell proliferation, apoptosis, and invasion by sponging miR-625 and miR-892b. *J Cell Biochem* 2019; **120**: 3780-3789 [PMID: 30382592 DOI: 10.1002/jcb.27658]
- 130 **Li J**, Li Z, Jiang P, Peng M, Zhang X, Chen K, Liu H, Bi H, Liu X, Li X. Circular RNA IARS (circ-IARS) secreted by pancreatic cancer cells and located within exosomes regulates endothelial monolayer permeability to promote tumor metastasis. *J Exp Clin Cancer Res* 2018; **37**: 177 [PMID: 30064461 DOI: 10.1186/s13046-018-0822-3]
- 131 **Li Z**, Yanfang W, Li J, Jiang P, Peng T, Chen K, Zhao X, Zhang Y, Zhen P, Zhu J, Li X. Tumor-released exosomal circular RNA PDE8A promotes invasive growth via the miR-338/MACC1/MET pathway in pancreatic cancer. *Cancer Lett* 2018; **432**: 237-250 [PMID: 29709702 DOI: 10.1016/j.canlet.2018.04.035]
- 132 **Shao F**, Huang M, Meng F, Huang Q. Circular RNA Signature Predicts Gemcitabine Resistance of Pancreatic Ductal Adenocarcinoma. *Front Pharmacol* 2018; **9**: 584 [PMID: 29922161 DOI: 10.3389/fphar.2018.00584]
- 133 **Liu Y**, Xia L, Dong L, Wang J, Xiao Q, Yu X, Zhu H. CircHIPK3 Promotes Gemcitabine (GEM) Resistance in Pancreatic Cancer Cells by Sponging miR-330-5p and Targets RASSF1. *Cancer Manag Res* 2020; **12**: 921-929 [PMID: 32104074 DOI: 10.2147/CMAR.S239326]
- 134 **Zhang HD**, Jiang LH, Sun DW, Hou JC, Ji ZL. CircRNA: a novel type of biomarker for cancer. *Breast Cancer* 2018; **25**: 1-7 [PMID: 28721656 DOI: 10.1007/s12282-017-0793-9]



Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-3991568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**Help Desk:** <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

