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Differential expression profiles of circRNAs in cancers: Future clinical and diagnostic perspectives

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Abstract

Since decades ago, circular RNAs (circRNAs) have been known for their critical role in RNA maturation, RNA transportation, epigenetic regulation, gene transcription, peptide/protein translation, and interaction with proteins to modulate their activities. At present, circRNAs are being extensively studied as oncotargets in the onset and development of several malignancies and treatment resistance by modulating various signaling pathways and cellular processes such as ubiquitination, degradation, invasion, proliferation, c-Myc oncoprotein stabilization, epithelial-mesenchymal transition, autophagy, and apoptosis. In addition, circRNAs are known to be highly conserved, have a longer life span than other RNAs, and their differential expressions are implicated in solid tumors and hematological malignancies. However, their potential diagnostic and therapeutic targets are not fully elucidated. Therefore, we sought to underline the opportunities and constraints associated with using these oncotargets in cancer therapy by outlining the functional mechanisms of circRNAs and their ectopic expression in distinct malignancies. The clinical applications of circRNAs in developing progressive markers like liquid biopsy biomarkers and for treating cancers are also prospected in this paper.

Keywords: CircRNAs; Upregulation; Down-regulation; Anticancer drugs resistance; Liquid biopsy biomarkers

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1. Introduction

Circular RNAs (circRNAs) are among the most thoroughly investigated ncRNAs in recent years, accounting for most of the human non-coding transcriptome[1,2]. Subsequent research has recognized the importance of circRNAs in regulating many cellular developmental and biological events, which involve critical molecular processes

such as chromatin modifications, DNA methylation, gene transcription, and messenger RNA (mRNA) destiny regulators splicing, translation, or decay[3-8].

Although circRNA biogenesis has been previously reviewed[9], the specific mechanisms of circRNAs formation are still poorly understood in terms of being explored and validated regularly. Most of the discovered exonic circRNAs (>90%) originated from protein-coding genes with one or several exons that have substantially longer intracellular half-lives, which implicates that circRNAs are resistant to exonuclease digestion[10-12]. Certain features of circRNAs include: (1) circRNAs are abundantly available in human fluids and tissues, and due to their stable covalently closed structure, certain circRNAs gather at a significant level compared to their canonical linear mRNAs[13]; (2) numerous circRNAs in eukaryotes are conserved evolutionarily[14]; and (3) many circRNAs are explicitly expressed in tissues or cells[14,15].

In addition, by competing for the particular miRNA, RNA species such as lncRNAs, pseudogene transcripts, mRNAs, and circRNAs that serve as competing endogenous RNAs (ceRNAs) affect genomic expression post-transcriptionally and impact the half-life or translation of target RNAs[16,17]. CircRNAs have been revealed to act like ceRNAs, regulating important biochemical events in cancer such as cell division, angiogenesis, and apoptosis. For example, it has been demonstrated that circRNAs can act as ceRNAs by controlling the expression of the GDNF family receptor alpha-1 (GFRA1) to change the expression of *miR-34a*, which subsequently inhibits the apoptosis of triple-negative breast cancer (TNBC)[17,18]. CircRNAs can also be utilized as RNA-binding protein (RBP) decoys to mediate its host gene expression or to subtly influence the activities of RBPs and associated proteins[14,19]. Furthermore, certain circRNAs containing IRES-like components and start codon (AUG) sites enable them to translate into particular small proteins/peptides[20].

Some circRNAs are obviously linked to cancer patients' clinical outcomes due to their crucial roles in biological pathways[21]. However, circRNAs can also play opposing roles to their linear counterparts. For example, the linear RNA of the human and mouse *ZBTB7A* genes works as a tumor suppressor, but the circRNA generated by *ZBTB7A* genes has a carcinogenic role in connective tissue malignancies[22]. On the other hand, the formation of *FOXO3*-encoded proteins, such as those caused by the mouse or human *FOXO3* gene, induces apoptosis and suppress tumor formation[23]. Moreover, circRNAs in exosomes and body fluids can serve as potential disease biomarkers[21,24,25].

Given the worth and interest of creating circRNAs-based knowledge, this paper aims to provide a detailed discussion on the functional mechanisms of circRNAs and their dysregulation in several cancers. In addition, this paper highlights the gaps, opportunities, and challenges in using circRNA-based approaches for cancer treatment. Moreover, the clinical applications of circRNAs in developing liquid biopsy biomarkers and identifying promising biomarkers for cancer diagnosis, prognosis, and therapy are also well discussed. Considering the need for literature and novelty aspects in this domain, we anticipate that the current review will be a resourceful addition of literature on circRNAs research and their future perspective regarding diagnosis and anticancer therapies.

2. Regulatory role of circRNAs in cancer

CircRNA altered expression is connected with diabetes, atherosclerosis, cardiovascular disease, and neurological illnesses based on its developing involvement in gene regulation[26]. However, recent research has demonstrated the aberrant production of circRNAs in several cell types of cancer, including gastric cancer (GC)[27], colorectal cancer (CRC)[28], hepatocellular carcinoma (HCC)[29], breast cancer (BC)[30], glioblastoma[31], and ovarian cancer (OC)[32]. Along the same lines, circRNAs participate in the modulation of many cellular signaling pathways, which can modulate tumorigenesis[33]. Most circRNAs have potential binding sites and act as sponges for the different miRNAs to regulate miRNA mediating the downstream activation of the target genes implicated in cancers. CircRNAs feature a covalently closed ring structure that is difficult to be degraded by cellular exonuclease degradation mechanism which typically readily recognizes the terminals of linear RNAs[12]. Exosomes are also enriched with stable circRNAs[25]. Considering the wide availability, cell-and-tissue-specific expression, and better stability, determining their function in human illness, particularly cancer, has been the main focus of many researchers.

2.1. BC

BC is a diverse illness and the world's most significant cause of mortality[34]. Evidence shows that oncogenic or tumor suppressor properties are influenced by circRNAs in BC[35,36]. Overexpression of circRNAs was found in estrogen-positive (ER+) adjacent normal tissues than in ER-negative tumor samples in the Cancer Genome Atlas (TCGA) database, implying that the frequency of circRNAs could serve as a possible cell proliferation indicator in BC[37]. Another highly expressed circRNA in BC, *circ-DNMT1* (hsa_circRNA_102439), was reported to increase cell proliferation and autophagy and inhibit senescence by binding directly to p53 and AUF1, resulting in the

promotion of nuclear translocation of these proteins[38]. Similarly, *FECR1*, a novel circular RNA generated from the FLI1 gene, regulates DNA methylation/demethylation of target genes to mediate BC cell metastasis[7,39]. In addition, the increase expression of circAGFG1 in TNBC increases cell proliferation, migration, invasion, tumor development, and metastasis by serving as ceRNA for *miR-195-5p* to diminish its target genes' inhibitory function[40,41].

On the contrary, *circFOXO3* is significantly lowered in BC tissues compared to the adjacent normal ones[36]. Abnormal *circ-FOXO3* triggers programmed death and prevents tumor cell development. On the other hand, overexpression of *circFOXO3* leads to the increase of its parental gene expression and upregulates the genes responsible for cell deaths. For example, *PUMA* inhibits p53 expression and promotes *MDM2*-induced p53 degradation. In addition, *circ-CCNB1* is significantly suppressed in BC. It has been demonstrated that *circ-CCNB1* in p53 mutant cells forms a compound with *H2AX* and *BCLAF1* mediating apoptosis[39]. In TNBC, the downregulation of *circTADA2A-E6* inhibits proliferation, motility, and infiltration. *circTADA2A-E6* serves as a *miR-203a-3p* sponge and restores the production of miRNA targeting the *SOCS3* gene, leading to the less invasive neoplastic phenotype. It concludes that circRNAs can mediate BC by acting as oncogenes or suppressors.

2.2. OC

OC is a highly aggressive tumor among gynecological malignancies and is primarily diagnosed in advance[42]. Multiple cancer-related signaling pathways, usually activated by linear mRNA, can be downregulated by circRNAs, indicating a potential role of circRNAs in tumor activation or inhibition[43]. CircRNAs exhibit differential expression among OC patients and healthy individuals, showing their potential roles as both the therapeutic and diagnostic biomarkers for this disease[44]. Ning *et al.* investigated circRNAs expression in EOC tissue samples and identified that 2556 circRNAs are upregulated, and 1832 circRNAs are downregulated compared with normal ovarian tissue samples[45]. Moreover, among the dysregulated circRNAs, *circEXOC6B* and *circN4BP2L2* were suggested to possess a potential prognostic disease-specific biomarker. Similarly, hsa_circ_0061140 has also been elevated in OC cells, which directly controls FOXM1 expression by binding to miR-370, thus promoting cell proliferation, migration, and epithelial-mesenchymal transition (EMT)[46]. However, *CircHIPK3* (hsa_circ_0000284) is substantially related to multiplication, motility, invasive, and apoptosis inhibition through binding to *miR-10-5p*[47].

2.3. GC

GC is a major source of mortality and a significant financial burden on health-care systems worldwide[48]. CircRNAs are reported to be stable in plasma and gastric juice, making them an ideal diagnostic marker for GC. Three circRNAs (has_circ_002059, hsa_circ_0000190, and circ-0001649) are variably expressed in the plasma of post-operative GC patients compared to pre-operative GC individuals. They are considerably downregulated in GC tissues compared to nearby tissues with average physiological properties[49]. The reduced expression of the above three circRNAs correlates significantly with gender, age, distal metastasis, and TNM stage[50-52]. However, circ*HIPK3*, but not *HIPK3* mRNA, is upregulated in GC and significantly affects cell proliferation. *CircHIPK3* expression is substantially higher than *HIPK3* mRNA, thus it demonstrates its crucial role as a product of pre-*HIPK3* mRNA[19]. *CircPVT1*, overexpressed in GC, has been identified to promote cell proliferation. Mortality risk and time without developing an illness positively correlate with its interaction with *miR-125* in GC patients[27]. *CircPVT1* mediates its function by upregulating c-Myc oncoprotein levels in GC cells and acts as a sponge for let-7b. CircRNAs are expressed differently, they interact with miRNAs through their binding sites to control the transcription of their downstream targets and may serve as a novel biomarker for GC[53].

2.4. CRC

A study showed a negative correlation between the total circRNAs abundance and cell proliferation in CRC, where its high expression suppressed cell proliferation[32]. The circ-ITCH was significantly lowered in CRC tissues. Its deficiency upregulated ITCH expression, which blocked the Wnt/beta-catenin pathway[54]. However, circ_0060745 was upregulated in CRC and linked with cellular propagation and metastasis through the sequestering of *miR-4736* and elevation of *CSE1L* levels[55]. Similarly, an analysis of 50 CRC tissue samples revealed that hsa_circ_0007142 is upregulated and linked with poor differentiation, and metastasis to the lymph nodes is mediated by its binding to miR-103a-2-5p[56]. Furthermore, circ-BANP is overexpressed in CRC tissues, and its silencing suppresses cellular multiplication[57]. Other circRNAs reported to be upregulated in CRC include *ciRS-7*[58], *circCCDC66*[28], and has_circ_0000069[59]. They are also associated with clinicopathological variables such as age and TNM stage. According to Zhang *et al.*'s research of the human circRNAs array in CRC tissues, hsa circRNAs 103809 and 104700 were dramatically downregulated and associated with lymph nodes, tumors, and distant metastasis[60]. CircRNAs are expressed differently to mediate cancer development.

2.5. HCC

Increasing evidence in scientific literatures implicate circRNAs in the development and progression of HCC, leading to a poor prognosis for HCC patients. For example, in comparison with neighboring normal liver tissue samples, hsa_circ_0001649 was significantly suppressed in 89 HCC tissue samples. In HCC, its expression was associated with both the size of the tumor and the tumor embolus, and knocking down the circRNA increased the mRNA level of matrix metallopeptidases (MMPs), promoting the spread of HCC[61]. Similar *circZKSCAN1* and its linear analog were suppressed in HCC tissues. Increased tumor size, cirrhosis, metastasis, and poor prognosis were linked to reduced expression of *circZKSCAN1*. Through several signaling pathways, the upregulation of *circZKSCAN1* and its linear mRNA can significantly prevent the growth and metastasis of HCC[62]. However, high expression of *circRHOT1* (hsa_circRNA_102034) in HCC tissue samples is associated with poor prognosis[63]. hsa_circ_100084 was more highly expressed in HCC clinical samples than in samples of healthy liver tissue. Sponging *miR-23a-5p* functions as a ceRNA to increase *IGF2* expression, enhancing HCC cell proliferation, invasion, and relocation[64]. Recently, Sun *et al.* observed three circRNAs (hsa_circ_0004001, hsa_circ_0004123, and hsa_circ_0075792) upregulated and positively correlated with tumor size and TNM stage in the blood of HCC patients. The underlying mechanism was the regulation of 35 distinct miRNAs by the Akt/mTOR, VEG, and Wnt signaling pathways[65].

2.6. Gliomas

Gliomas are a vast category of nervous system tumors and one of the most prevalent malignancies with a poor prognosis globally. Recent studies have revealed the transcription of circRNAs in mammalian brains and their role in the growth and spread of gliomas[66]. A total of 476 circRNAs with differential expression have been found in 46 GBM and normal brain tissue samples, among which 468 circRNAs were more upregulated in normal brain tissue than GBM tissues. Furthermore, eight circRNAs, including *circCOL1A2*, *circPTN*, *circVCAN*, *circSMO*, *circPLOD2*, *circGLIS3*, *circEPHB4*, and *circCLIP2*, had significantly higher expression in glioblastoma multiforme (GBM) samples compared to normal human tissues, raising the possibility that they could be used as biomarkers for the disease[67]. The oncogenic circRNA, *cZNF292*, influences the development of tube formation. By controlling the Wnt/beta-catenin biochemical pathway, the suppression of *cZNF292* prevents glioma cell proliferation, progression, and tube formation[68]. Another study determined differentially expressed (206 upregulated and 1205 downregulated) circRNAs in GBM patients and found a significant association between circRNAs with low expression and the development of GBM through ErbB and neurotrophin signaling pathways[69]. Besides, common expression of *circBRAF* has been identified in glioma patients with high-grade tumors[68]. However, *circTTBK2* has a higher expression in glioma tissues. Its effect is induced by impairing miR-217 and elevating HNF1β expression, which subsequently binds to Derlin-1 oncogene, thereby increasing its promoter activity and upregulating the cell proliferation, migration, and apoptotic repression by targeting PI3K/Akt and ERK signaling pathways[70]. Similarly, hsa_circ_0000177 also causes an increased expression of glioma tissues, which is linked to the poor prognosis of patients. The silenced hsa_circ_0000177 acts as a *miR-638* sponge to drastically reduce cell growth and metastasis. This causes the frizzled class receptor 7 (FZD7) to be upregulated, further regulating Wnt signaling and enhancing glioma cell development[71]. *CircMMP9* also has high expression in glioma cancer. Through *miR-124* sponging, increased expression of *circMMP9* regulates CDK4 and Aurora kinase A (AURKA), and glioblastoma multiforme cells are driven to proliferate, migrate, and invade[72]. Moreover, *circPRKCI* is overexpressed in glioma tissues and significantly stimulates *miR-545*, inhibiting cancer growth, survival, multiplication, and relocation[31]. Similarly, circ_001350 is highly expressed in tissue samples and cells from glioma patients, and by interacting with *miR-1236*, it reduces cell growth and metastasis while promoting apoptosis[73]. *Circ-MAPK4* (hsa_circ_0047688) upregulated and associated with a pathogenic form of gliomas, has been shown to impede the apoptosis of glioma cells by acting as a sponge of miR-125a-3p and regulating p38/MAPK signaling pathway[74].

2.7. Pancreatic ductal adenocarcinoma (PDAC)

More than 85% of cases of pancreatic cancer are caused by PDAC, which is also one of the main causes of death and poor prognosis globally[75]. Numerous circRNAs that are overexpressed in PDAC have been identified. It is crucial to find these circRNAs that express differently to better comprehend PDAC. In PDAC cancer patient samples, Li *et al.* discovered seven circRNAs using circRNA microarray analysis, of which two had upregulated expression levels and the remaining five had downregulated expression levels[76]. A total of 278 circRNAs were differentially expressed in PDAC tissues according to RNA sequencing and circRNA expression analysis. Among these, hsa_circ_0007334 was strongly upregulated and acts as a ceRNA by binding to *miR-144-3p* and *miR-577*, which boosted the expression and functionality of *MMP7* and collagen type I alpha 1 chain (*COL1A1*) in PDAC[77]. Likewise, pancreatic cancer (PC) tissues had higher levels of *circLDLRAD3*, which

was associated with a poor prognosis for PC patients. *CircLDLRAD3* directly binds to *miR-137-3p* as a sponge and promotes cellular multiplication, relocation, and infiltration of PC cells through targeting pleiotrophin (PTN)[78]. Chen *et al.* discovered 12,572 circRNAs in the exosomes of irradiated human PC cells using RNA-sequencing analysis. There were 196 circRNAs that showed varied expression and were connected to methylation. In addition, the upregulated gene hsa_circ_0002130 interacted with *miR-4482-3p* to enhance NBN expression, lowering the survival rate in PC patients[79]. Binding to *miR-34b-5p*, upregulating mesenchymal-epithelial transition factor, and phosphorylating Akt, a new circRNA (*circBFAR*, hsa_circ_0009065) derived from exon 2 of the *BFAR* gene, upregulated in 208 PDAC patients, was demonstrated to accelerate PDAC cells progression (Ser 473)[80]. *CircFOXK2* was upregulated in PDAC tissue samples according to another study. It stimulates Ankyrin 1 (*ANK1*), glial cell-derived neurotrophic factor (GDNF), paired box 6 (PAX6), NUF2 component of NDC80 kinetochore complex (NUF2), pyridoxal kinase (PDXK), Y-box-binding protein 1 (YBX1), and heterogeneous nuclear ribonucleoprotein K (hnRNPK) expression, as well as cell expansion, migratory property, and colony formation[81].

2.8. Lung cancer (LC)

Most deaths resulting from cancer are attributable to LC worldwide. The development of LC can be controlled by inappropriate circRNAs expression. In non-small-cell LC (NSCLC) tissue samples, *ciRS-7* was upregulated and was associated with a higher TNM stage, lymph node metastases, and a shorter overall survival time. Overexpressed *ciRS-7* inhibits *miR-7*, which causes the *EGFR*, *CCNE1*, and *PIK3CD* to be upregulated to promote cellular proliferation and prevent LC apoptosis[82]. Hsa_circ_0012673 upregulates lung adenocarcinoma (LAC) tissues compared to non-tumor tissues. The hsa_circ_0012673 promotes LAC cell propagation by inhibiting the expression of *miR-22* and targeting the erb-b2 receptor tyrosine kinase 3 (*ErbB3*)[83]. Similarly, increased expression of hsa_circ_0020123 in NSCLC tissues is connected to poor differentiation, lymph node metastases, and advanced TNM stage, all associated with malignancy. The inhibition of *miR-144* and the increase in the expression of *ZEB1* and *EZH2* encourages NSCLC cell proliferation, migration, and invasion[84]. *CircAGFG1*, another circRNA upregulated in NSCLC tissues, promotes cell proliferation and metastasis by suppressing *miR-203* and activating *ZNF281*[85]. The most current microarray research shows that the highly expressed new circRNA, *circSLC25A16* (hsa_circ_0018534), stimulates lactate dehydrogenase A and *sponges miR-488-3p/HIF-1* to activate glycolysis and promote cell growth in NSCLC cells (LDHA)[86]. In addition, circRNAs such as *circRNA 102231*, *circRNA 100146*, *circFARSA*, and *circPVT1* are elevated in NSCLC and enhance the advancement of NSCLC[87-91]. Therefore, these circRNAs may be employed as promising diagnostic and prognostic indicators to identify LC.

2.9. Prostate cancer (PCa)

PCa is among the main risk factors in males due to cancer-related causes[92]. A study conducted by Xia *et al.* found 1021 circRNAs with differential expression (117 upregulated and 904 downregulated) in PCa tissues sample and cell lines. Some circRNAs were overexpressed in PCa tissues and connected to PCa pathogenesis, specifically hsa_circ_0057558 and hsa_circ_0062019. While hsa_circ_0062019 operates as a sponge for *miR-5008-5p* to control the folate level and the development of PCa, hsa_circ_0057558 functions as a sponge for miR-6884-*3p*, thereby preventing lipid metabolism by supporting its downstream target genes[93]. Moreover, downregulation of hsa_circ_0004870 and its host gene, *RBM39*, in enzalutamide-resistant cells suggests that they play a critical role in the progression of castration-resistant PCa that is resistant to enzalutamide[94]. In addition, PCa tissues and serum samples had higher levels of *circFOXO3*, and its silencing prevented mitosis and promoted programmed cell death by acting as a reservoir for *miR-29-3p* and upregulated the expression of *SLC25A15*[95]. Through bioinformatics research, Wu *et al.* screened 60 circRNAs that were differentially expressed in PCa and healthy samples: One circRNA, hsa_cir_0024353, was downregulated; and two circRNAs, hsa_circ_0031408 and hsa_circ_0085494, were found to be upregulated among the differentially expressed circRNAs. These three circRNAs affect a number of metabolic processes, including phosphoinositide 3-kinase-Akt, P53, and hypoxia-inducible factor-1[96]. Another study discovered 749 circRNAs differentially expressed in PCa tumor and paracancerous tissues. Among them, 261 were upregulated in PCa tissues, whereas 487 were downregulated. According to analyses by KEGG pathways and gene ontologies, numerous circRNAs are connected to cancer development. The most significant alterations among the differentially expressed circRNAs were in hsa_circ_0033074 and hsa_circ_0016064[97]. Moreover, PCa cells proliferate and invade when *circHIPK3* is upregulated and acts as a miR-339-3p sponge, while circRNA *ITCH* works as a *miR-17-5p* sponge and slows PCa growth by increasing *HOXB13* expression[98,99].

2.10. Hematological malignancies

Hematological malignancies are life-threatening cancers that originate from genetic and epigenetic abnormalities[100].

Acute myeloid leukemia, chronic myeloid neoplasms, chronic lymphocytic leukemia (CML), B- and T-cell lymphoma, and multiple myeloma (MM) are hematological malignancies that exhibit circRNA expression. Hsa_circ_0004277 was downregulated in AML samples as opposed to controls and post-treatment subjects. By acting as a sponge for *miR-138-5p* and *miR-30c-1-3p*, hsa_circ_0004277 controls the expression of downstream genes implicated in cancer development[101]. *CircPVT1* was increased in acute myeloid leukemia compared to normal bone marrow cells, and it was discovered that it acts as a sponge for the miRNA *let-7*, showing that it might be a viable treatment focus for the disease[102]. Several circRNAs with abnormal expression in CML have been identified using high-throughput sequencing technology. Among these circRNAs, hsa_circ_0080145 was significantly overexpressed and can effectively bind to *miR-29b* to regulate cell proliferation in CML[103]. Besides, *circ-CBFB* was overexpressed in CLL patients' samples compared to normal controls. It promotes cell cycle progression and reduction by inhibiting *miR-607*, facilitating *FZD3* expression, and activating the Wnt/b-catenin pathway in CLL[104]. By performing RNA sequencing profiling, Dahl *et al.* recently identified a novel overexpressed circRNA from the *IKZF3* gene with oncogenesis functions[105,106].

Several other differentially expressed circRNAs have also been studied, and their upregulation is associated with the progression of different cancers. For instance, *circTCF25* in bladder cancer[107], hsa_circ_100855 in laryngeal cancer[108], *circUBAP2* in osteosarcoma[109], *circ-ZNF609* in renal cell carcinoma[110], *circSLC30A7* in oral squamous cell carcinomas[111], and all of which are upregulated and involved in the progression of cancers. In contrast, *Cir-ITCH* is less expressed in esophageal squamous cell carcinoma than in the adjacent normal tissues[50]. Therefore, based on the widespread presence of circRNAs in various parts of the human body, it is logical to propose that circRNAs can be used in cancer diagnosis.

3. CircRNAs as diagnostic biomarkers for cancer

Different sampling strategies can be used to diagnose the etiologic modulator of cancer. In a liquid biopsy, body fluid was used as a sample for diagnosis or the development of human diseases instead of tissue biopsy, with the advantages of being less intrusive, accurate, easy assessments, time serving, and with a lower morbidity rate[112]. Several liquid biopsy biomarkers have been proved helpful in the diagnosis of various malignancies, including cell-free DNA[113], circulating tumor DNA[112], and cell-free RNA[113-115]. NcRNAs, particularly circRNAs, have demonstrated significant potential as circulating diagnostic biomarkers for liquid biopsy using cell-free RNA-based liquid biopsy. CircRNAs have several essential features including stability, specificity, conservation, and abundance in bodily fluid, making them valuable biomarkers for human diseases, including cancer. CircRNAs can be found in various human body fluids, including saliva, brain/spinal fluid, blood, urine, free-floating cells (such as circulating blood cells/tumor cells), and exosomes[112,114,116]. Circulating cell-free RNAs released by various tissues and cells can be recognized in serum, plasma, and blood. In addition, the stability of circRNA is an important factor, leading to potential target for many diseases[117]. As a result, cell-free circRNAs have tissue-specific features, emphasizing their clinical significance for the respective tissues[118]. Microarray, NanoString technology, digital droplet PCR (ddPCR), or next-generation sequencing (NGS) technologies can be used to quantify circRNAs derived from different body fluids, circulating blood cells, or exosomes for early diagnosis, disease development and monitoring, or precise therapy selection for different types of cancers (Figure 1)[119-121]. In liver cancer cells and cell-derived exosomes, a 2-fold enrichment of circRNAs was recently discovered in exosomes compared to parental cells, and the expression can be persistent in serum after incubation at room temperature for up to 24 h[25]. *circFMN2* and *circIFT80* have recently been shown to be highly overexpressed in serum exosomes and have been linked to cell proliferation, invasion, and inhibition of apoptosis through the *circFMN2/miR-1182/hTERT* axis and the *circIFT80/miR-1236-3p/HOXB7* axis, respectively[122,123]. Cell-free circRNAs' roles in human bodily fluids and their implications in numerous diseases might be used as liquid biopsy biomarkers to identify tumors at an early stage. Table 1 enumerates the circRNAs identified to be dysregulated in different human body fluids.

4. CircRNAs involved in drug resistance

Many studies have linked ncRNAs (lncRNAs and miRNAs) to chemoresistance[150,151], paucity of data is available on the regulatory mechanisms of circRNAs in developing drug resistance in malignancies. Some studies have recently looked at the function of circRNAs in resistance to various anticancer medicines (chemotherapeutic drugs, targeted therapies, and immunotherapeutic drugs) in terms of concentration of drug, downstream signaling pathway regulation, and DNA repair ability[152,153]. Drug resistance phenotypes can have two mechanisms: intrinsic or acquired, depending on whether they were innately resistant to treatment or tolerated after drug exposure. Due to their high differentiation rates, cancer stem cells can also drive acquired resistance. As a result, tumor heterogeneity,

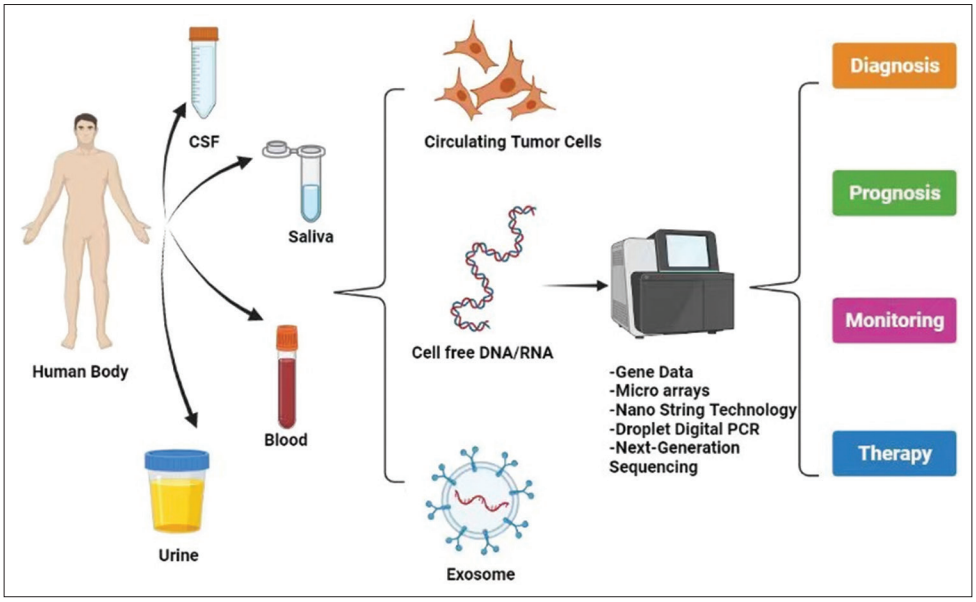

Figure 1. Orientation of circRNAs as a diagnostic biomarker for cancers through liquid biopsy. Using body fluids and other molecular biomarkers, effective management strategies for cancer diagnostic screening. The body fluids of cancer patients contain disease-specific circulating free DNA/RNA, circRNAs, and circulating tumor cells. Various molecular biology techniques, such as digital droplet PCR, NanoString technology, microarrays, and next-generation sequencing, can be used to analyze the nucleic acid extracted from a sample of body fluids.

EMT, drug transport and metabolism, autophagy, and apoptosis inhibition enhance drug resistance[154]. CircRNAs interact with these molecules and modify them to promote drug resistance[155].

Various drug response pathways, such as PI3K/AKT, MAPK, VEGFR, MEK/ERK, and the ATP-binding cassette (ABC) transport system, are regulated by circRNAs as well[156]. According to a recent study, *circNFIX* was overexpressed in temozolomide-resistant glioma individuals and conferred temozolomide resistance to recipient glioma cells through exosomes through inhibiting *miR-132*[151]. *CircPVT1* promotes treatment resistance to doxorubicin and cisplatin in osteosarcoma tissues, blood, and chemoresistant cell lines by increasing the expression of the *ABCB1* gene[157]. Furthermore, through the *miR-182-5p/FOXO3a* axis, hsa_circ_0025202 overexpression is frequently downregulated in BC tissues and tamoxifen-resistant cell lines, reduces cell division and movement, boosts cell apoptosis, and improves tamoxifen sensitivity[158]. The above findings suggest that circRNAs perform a vital part in chemoresistance. Figure 2 depicts certain anticancer drug-resistant circRNAs in various malignancies.

5. Implementation of new models in circRNA cancer research

The significance of circRNAs in the pathophysiology of specific cells is being studied using two-dimensional and three-dimensional cellular systems as research platforms. Due to their ability to faithfully mimic the evolution of cancer, inducible systems that overexpress genes are valuable models for observing circRNA expression and changes during tumor progression in two-dimensional biological systems[159]. In addition, to gain crucial knowledge about the pathways and processes impacted by circRNA entities, it is possible to experimentally assess the impact of circRNAs' potential qualitative/quantitative variations on other properties, such as RBPs and miRNAs. Similarly, three-dimensional cellular systems, including brain organoids made from iPSCs[159], have already been used in circRNA research. About 56% of the detected circRNAs in those organoid cultures overlapped circRNAs from the postmortem brain[160]. The highest in terms of ability and similarity to the original tissue are patient-derived organoids, indicating their broad applications in various malignancies, including GC[161-166]. Other approaches for studying circRNAs include animal models with manipulable loci encoding these molecules. Sensorimotor gating was disturbed in mice with a deletion in the *Cdr1* as circRNA gene, which substantially binds *miR-7* and *miR-671*, leading in neuropsychiatric problems due to the animals' inability to filter out redundant data[165]. In addition, a study utilized shRNAs to selectively downregulate five highly expressed circRNAs in *Drosophila* by targeting particular circRNA-back-splice junctions[166]. The downregulation of *circ–Ctrip* resulted in developmental lethality. These examples highlight

Table 1. circRNAs dysregulated in several cancers and also found in body fluids.

Cancer type	circRNA	Expression in disease	Body fluid	Function	Pathway/ miRNA sponge	Pathological status	Cases/ controls	References
BC	hsa_ circ_0001785	Up	Plasma	The expression level decreases significantly in post-operative patients than pre-operative patients. A potential biomarker for early detection of BC	-	Associated with histological grade, TNM stage, and DS	57/17	[124]
TC	hsa_ circ_007293, hsa_ circ_031752, and hsa_ circ_020135	Up	Serum exosomes	Potential diagnostic, prognostic, or therapeutic biomarkers	PI3K-Akt and AMPK signaling pathway	-	3/3	[125]
OC	*circMAN1A2*	Up	Serum	Could be a good diagnostic biomarker for malignant tumor	*miR-135a-3p*	-	36/121	[126]
	hsa_ circ_0001068	Up	Serum exosomes	Non-invasive biomarker for the diagnosis and treatment of OC	*miR-28-5p*	-	95/53	[127]
EC	hsa_ circ_0109046 & hsa_ circ_0002577	Up	Serum	EVs circRNAs served as biomarkers for EC diagnosis	Involved in multiple pathways	-	10/10	[128]
CRC	*circIFT80*	Up	Serum exosomes	Promotes CRC cell growth, proliferation, migration, and invasion	*circIFT80/miR-1236-3p/HOXB7*	Associated with advanced tumor stage and DS	58/58	[123]
	hsa_ circ_0001649	Down	Serum	A potential biomarker for CRC patients	-	Associated with pathological differentiation	64/64	[129]
	circVAPA	Up	Plasma	Promotes cell proliferation, migration, invasion, and inhibit apoptosis	*miR-101*/KEGG pathway	Associated with LNM, DS, and TNM stage	60/60	[130]
	circFMN2	Up	Serum exosomes	Promotes cell proliferation and migration	*circFMN2/miR-1182/hTERT*	Associated with tumor size, advanced tumor stage, DS, and TNM stage	88/88	[122]
	circ-CCDC66, circ-ABCC1 and *circ-STIL*	Down	Plasma	Promotes tumor growth and progression	-	No association observed	45/61	[131]
	hsa_ circ_0004771	Up	Serum	Associated with clinicopathological factors of GC patients	-	Associated with DS and TNM stage	110/70	[132]
GC	hsa_ circ_0000190	Down	Plasma	Associated with clinicopathological factors of GC patients	-	Associated with tumor diameter, LNM, DS, and TNM stage	104/014	[51]
	hsa_ circ_0000745	Down	Plasma	Might be a novel potential biomarker for diagnosing of GC	Bind to various miRNAs	Associated with TNM stage	60/60	[133]
	hsa_ circ_0001017, hsa_ circ_0061276	Down	Plasma	Associated with pathological factors and predictor for early diagnosis, prognosis of GC	-	Associated with higher mortality and TNM stage	121/121	[134]
	hsa_ circ_0000467	Up	Plasma	Promotes proliferation, migration, and invasion	Bind to various miRNAs	Associated with TNM stage	51/51	[136]
LC	*circFARSA*	Up	Plasma	Promotes cell migration and invasion	*miR-330-5p* and *miR-326*	No significant differences observed	10/10	[91]

(Cont'd...)

Table 1. ***(Continued).***

Cancer type	circRNA	Expression in disease	Body fluid	Function	Pathway/ miRNA sponge	Pathological status	Cases/ controls	References
UCB	*circPRMT5*	Up	Serum and urine exosomes	Promotes metastasis and aggressiveness of USB cells	Promotes EMT via circPRMT5/ *miR-30c*/SNAIL1/ E-cadherin	Associated with advanced tumor stage and worse patient survival	119/119	[137]
NPC	*circMAN1A2*	Up	Serum	Could be good diagnostic biomarker for malignant tumor	*miR-135a-3p*	-	100/121	[126]
	hsa_ circ_0000285	Up	Serum	Possibly regulates cell proliferation, metastasis, and radio sensitivity	*miR124*	Associated with tumor size, differentiation, LNM, DS, and TNM stage	150/100	[138]
ALL	*circPVT1*	Up	BM	Promotes proliferation and apoptosis	Through c-Myc and Bcl-2 expression in ALL	No significant differences observed	48/40	[139]
CLL	*circ-COX2*	Up	Plasma exosomes	Promotes CLL progression and prognosis	-	-	54/40	[140]
MM	*circMYC*	Up	Exosomes	Expression level circMYC associated with deletion 17p	-	Associated with higher relapse and mortality rates	122/54	[141]
	hsa_ circ_0007841	Up	BM plasma	Promote cell proliferation, cell cycle, metastasis, and inhibits apoptosis	Through the activation of PI3K/Akt signaling through *miR-338-3p*/ *BRD4* axis	-	41/41	[142]
HCC	*circSMARCA5*	Down	Plasma	Promotes proliferation, invasion, metastasis, and inhibits apoptosis	-	Associated with tumor differentiation and TNM stage	133/33	[143]
	circ-DB	Up	Plasma	Promotes rapid tumor progression by targeting deubiquitination-related USP7	*miR-34a*/ USP7/ Cyclin A2 signaling pathway	-	-	[144]
	circUHRF1	Up	Plasma	Decreases NK cell proportion and NK cell tumor infiltration and associated with poor prognosis	Through degradation of *miR-449c-5p*/ TIM-3	Associated with tumor size	240/240	[145]
PC	*circ-LDLRAD3*	Up	Plasma	Associated with venous, lymphatic invasion, and metastasis	-	No association found with pathological factors	31/31	[146]
OSCC	hsa_ circ_0001874, hsa_ circ_0001971,	Up	Salivary	The expression level decreases in the post-operative samples than pre-operative samples	*miR-107* and *miR-103a-3p*	Associated with TNM stage and tumor grade	163/85	[147]
OS	hsa_ circ_0000885	Up	Serum	High expression level associated with lower rates of disease-free survival and overall survival	-	Associated with Enneking stage IIB or III osteosarcoma and lung metastasis	50/50	[148]
LAC	hsa_ circ_0013958	Up	Plasma	Promotes cell proliferation and invasion and inhibited cell apoptosis	*miR-134*	Associated with TNM stage and LNM	49/49	[149]

BC: Breast cancer; TNM: Tumor node metastasis; DS: Distant metastasis; LNM: Lymph node metastasis; TC: Thyroid cancer; OC: Ovarian cancer; EC: Endometrial cancer; EVs: Extracellular vesicles; CRC: Colorectal cancer; GC: Gastric cancer; LC: Lung cancer; UCB: Urothelial carcinoma of the bladder; NPC: Nasopharyngeal carcinoma; ALL: Acute lymphoblastic leukemia; BM: Bone marrow; CLL: Chronic lymphocytic leukemia; MM: Multiple myeloma; HCC: Hepatocellular carcinoma; PC: Pancreatic cancer; OSCC: Oral squamous cell carcinoma; OS: Osteosarcoma; LAC: Lung adenocarcinoma

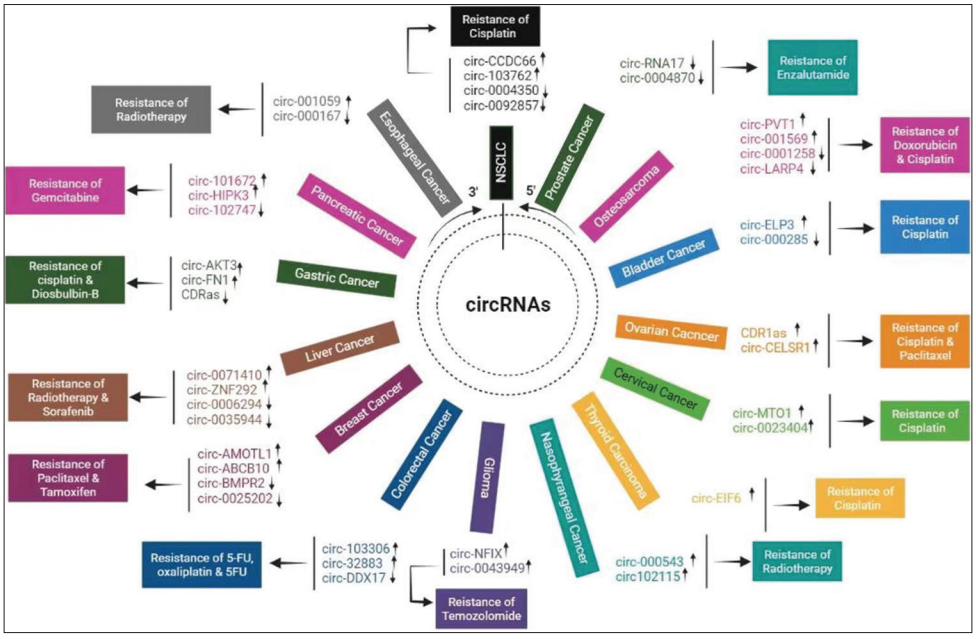

Figure 2. Anti-cancers drug-resistant circRNAs in various malignancies. Differential expression of each circRNA promotes the resistance to one or multiple drugs results in activation of the respective pathway and affects anticancer treatment efficacy, by altering cancer cell properties and/or drug distribution. The illustrated circRNAs act mainly as miRNA sponges, leading to up-/down-regulation of the downstream targets of these miRNAs. Other modes of action of circRNAs affecting the expression of key proteins implicated in therapy resistance.

the importance of such procedures and provide crucial information on how circRNAs function and are active.

6. CircRNAs: Toward a unified nomenclature

CircRNAs are becoming essential indicators of disease, particularly in cancer, necessitating a unified naming scheme. In addition, developing new biochemical methods and bioinformatic methodologies add to the evidence for distinguishing and classifying circRNAs. The current terminology is based on circBase, which includes a numeric code and species information. In contrast, circBank and circles build a circRNA annotation based on UCSC genomic coordinates (https://genome.ucsc.edu/) using the gene symbol of the transcript. CIRCpedia uses a distinctive name scheme that incorporates both the species and a circBase internal identification number. In addition, circRNAs have been classified using a unique vocabulary. The species is indicated by the first few letters of the gene name, the exons involved in the circularization, and the gene name: For example, exons of the hsa-circ gene (exons7-8)[167].

7. Conclusion and perspectives

circRNAs have a wide range of functional possibilities due to their active roles as miRNA sponges, RBP sponges, and transcriptional regulators in the modulation of protein-coding gene expression. The fact that circRNAs are abundantly available in saliva, exosomes, and blood samples makes them promising biomarkers for disease diagnosis, particularly for the onset, progression, and prognosis of cancer. Identification of circRNA biomarkers in blood and saliva and in other clinical samples such as urine and cerebrospinal fluid would be feasible in further research. More crucially, research on circRNAs opens up a new path for treating diseases, with the circularization of RNA being the eventual goal for treating illness. For instance, in the future, the overexpression of artificial circRNA can function as a "super-sponge" or can be used to silent the circRNAs in cells to remodel and alter the expression profile of miRNAs and other RNAs, or RBP levels can increase the activities of a suppressor gene in the context of cancer therapy. Although circRNAs have been the subject of several research studies, little is known about the biological and molecular processes by which circRNAs contribute to cancer development. Therefore, finding numerous additional circRNAs implicated in diseases and investigating their functional motifs and target locations will be essential.

The practical use of circRNAs in clinics still has a long way to go as the field of circRNA research is still in its infancy. CircRNAs alone will not be sufficient to serve as precise biomarkers for any particular malignancy. Despite some reports that certain circRNAs are specific for individual cancers, the level of these circRNAs in the other cancer types has not been determined by any studies, and this underlies the current uncertainty and specificity of

these circRNAs for a particular cancer type. Theoretically, although circRNA acts as a miRNA sponge, the miRNA may target several genes, indicating that a circRNA may modulate the expression of hundreds of genes. As a result, it is doubtful that a circRNA would be entirely specific for a particular cancer type. The most likely scenario is that circRNAs are either a common driving mechanism or by- or end-product of oncogenesis.

However, circRNAs may still be valuable as cancer biomarkers, just not for a particular type of cancer. In clinical settings, diagnosing specific cancer depends on clinical phenotypes and other data to analyze a particular malignancy. According to this, circRNAs could benefit in diagnosing several malignancies if combined with other factors or biomarkers.

In conclusion, circRNAs are a type of regulatory RNA that are highly expressed and functionally involved in cellular processes, suggesting that they may have a role in the emergence of several disorders, including cancer. Due to their ectopic expression in cancer, the current research has established that these circRNAs are essential in designing the approaches to investigate them in diagnosis and anticancer therapies. In this paper, we highlight and urge the design of advanced techniques to evaluate the critical roles of circRNAs in modulating cellular processes such as cell proliferation, migration, invasion, apoptosis, and autophagy for a better picture of their involvement in cancer development. Considering the critical applications of circRNAs and the potential to provide the template for designing anticancer drugs, we anticipate that using circRNAs in clinical sittings will shortly lead to a breakthrough in cancer therapy.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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References

1. Mercer TR, Dinger ME, Mattick JS, 2009, Long non-coding RNAs: Insights into functions. *Nat Rev Genet*, 10(3):155–159.

   https://doi.org/10.1038/nrg2521

2. Consortium EP, 2012, An integrated encyclopedia of DNA elements in the human genome. *Nature*, 489, 57–74.

3. Pelechano V, Steinmetz LM, 2013, Gene regulation by antisense transcription. *Nat Rev Genet*, 14(12): 880–893.

   https://doi.org/10.1038/nrg3594

4. Memczak S, Jens M, Elefsinioti A, *et al.*, 2013, Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*, 495(7441): 333–338.

   https://doi.org/10.1038/nature11928

5. Conn SJ, Pillman KA, Toubia J, *et al.*, 2015, The RNA binding protein quaking regulates formation of circRNAs. *Cell*, 160(6): 1125–1134.

   https://doi.org/10.1016/j.cell.2015.02.014

6. Huang C, Shan G, 2015, What happens at or after transcription: Insights into circRNA biogenesis and function. *Transcription*, 6(4): 61–64.

   https://doi.org/10.1080/21541264.2015.1071301

7. Chen N, Zhao G, Yan X, *et al.*, 2018, A novel FLI1 exonic circular RNA promotes metastasis in breast cancer by coordinately regulating TET1 and DNMT1. *Genome Biol*, 19(1): 218.

   https://doi.org/10.1186/s13059-018-1594-y

8. Zhao X, Cai Y, Xu J, 2019, Circular RNAs: Biogenesis, mechanism, and function in human cancers. *Int J Mol Sci*, 20(16): 3926.

   https://doi.org/10.3390/ijms20163926

9. Khan FA, Nsengimana B, Khan NH, *et al.*, 2022, Chimeric peptides/proteins encoded by circRNA: An update on mechanisms and functions in human cancers. *Front Oncol*, 12: 781270.

   https://doi.org/10.3389/fonc.2022.781270

10. Salzman J, Gawad C, Wang PL, *et al.*, 2012, Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One*, 7: e30733.

    https://doi.org/10.1371/journal.pone.0030733

11. Guo JU, Agarwal V, Guo HL, *et al.*, 2014, Expanded identification and characterization of mammalian circular RNAs. *Genome Biol*, 15: 409.

    https://doi.org/10.1186/s13059-014-0409-z

12. Naeli P, Pourhanifeh MH, Karimzadeh MR, *et al.*, 2020, Circular RNAs and gastrointestinal cancers: Epigenetic regulators with a prognostic and therapeutic role. *Crit Rev Oncol Hematol*, 145: 102854.

    https://doi.org/10.1016/j.critrevonc.2019.102854

13. Lim TB, Lavenniah A, Foo RS, 2020, Circles in the heart and cardiovascular system. *Cardiovasc Res*, 116(2): 269–278.

    https://doi.org/10.1093/cvr/cvz227

14. Jeck WR, Sorrentino JA, Wang K, *et al.*, 2013, Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA*, 19(2): 141–157.

    https://doi.org/10.1261/rna.035667.112

15. Patop IL, Wüst S, Kadener S, 2019, Past, present, and future of circRNAs. *EMBO J*, 38: e100836.

    https://doi.org/10.15252/embj.2018100836

16. Zhong Y, Du Y, Yang X, *et al.*, 2018, Circular RNAs function as ceRNAs to regulate and control human cancer progression. *Mol Cancer*, 17(1): 79.

    https://doi.org/10.1186/s12943-018-0827-8

17. Nsengimana B, Khan FA, Awan UA, *et al.*, 2022, Pseudogenes and liquid phase separation in epigenetic expression. *Front Oncol*, 12: 912282.

    https://doi.org/10.3389/fonc.2022.912282

18. He R, Liu P, Xie X, *et al.*, 2017, circGFRA1 and GFRA1 act as ceRNAs in triple negative breast cancer by regulating miR-34a. *J Exp Clin Cancer Res*, 236(1): 145.

    https://doi.org/10.1186/s13046-017-0614-1

19. Zheng Q, Bao C, Guo W, *et al.*, 2016, Circular RNA profiling reveals an abundant circhipk3 that regulates cell growth by sponging multiple miRNAs. *Nat Commun*, 7: 11215.

    https://doi.org/10.1038/ncomms11215

20. Ashwal-Fluss R, Meyer M, Pamudurti NR, *et al.*, 2014, circRNA biogenesis competes with Pre-mRNA splicing. *Mol Cell*, 56(1): 55–66.

    https://doi.org/10.1016/j.molcel.2014.08.019

21. Kristensen LS, Hansen TB, Venø MT, *et al.*, 2018, Circular RNAs in cancer: Opportunities and challenges in the field. *Oncogene*, 37(5): 555–565.

    https://doi.org/10.1038/onc.2017.361

22. Guarnerio J, Zhang Y, Cheloni G, *et al.*, 2019, Intragenic antagonistic roles of protein and circRNA in tumorigenesis. *Cell Res*, 29(8): 628–640.

    https://doi.org/10.1038/s41422-019-0192-1

23. Yang W, Du WW, Li X, *et al.*, 2016, Foxo3 activity promoted by non-coding effects of circular RNA and Foxo3 pseudogene in the inhibition of tumor growth and angiogenesis. *Oncogene*, 35(30): 3919–3931.

    https://doi.org/10.1038/onc.2015.460

24. Lasda E, Parker R, 2016, Circular RNAs co-precipitate with extracellular vesicles: A possible mechanism for circRNA clearance. *PLoS One*, 11(2): e0148407.

    https://doi.org/10.1371/journal.pone.0148407

25. Li Y, Zheng Q, Bao C, Li S, *et al.*, 2015, Circular RNA is enriched and stable in exosomes: A promising biomarker for cancer diagnosis. *Cell Res*, 25(8): 981–984.

    https://doi.org/10.1038/cr.2015.82

26. Haque S, Harries LW, 2017, Circular RNAs (circRNAs) in health and disease. *Genes* (*Basel*), 8(12): 353.

    https://doi.org/10.3390/genes8120353

27. Chen J, Li Y, Zheng Q, *et al.*, 2017, Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer. *Cancer Lett*, 388: 208–219.

    https://doi.org/10.1016/j.canlet.2016.12.006

28. Hsiao KY, Lin YC, Gupta SK, *et al.*, 2017, Noncoding effects of circular RNA CCDC66 promote colon cancer growth and metastasis. *Cancer Res*, 77(9): 2339–2350.

    https://doi.org/10.1158/0008-5472.CAN-16-1883

29. Huang XY, Huang ZL, Xu YH, *et al.*, 2017, Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-100338/miR-141-3p pathway in hepatitis B-related hepatocellular carcinoma. *Sci Rep*, 7(1): 5428.

    https://doi.org/10.1038/s41598-017-05432-8

30. Wang S, Xue X, Wang R, *et al.*, 2018, CircZNF609 promotes breast cancer cell growth, migration, and invasion by elevating p70S6K1 via sponging miR-145-5p. *Cancer Manag Res*, 10: 3881–3890.

    https://doi.org/10.2147/CMAR.S174778

31. Zhang X, Yang H, Zhao L, *et al.*, 2019, Circular RNA PRKCI promotes glioma cell progression by inhibiting microRNA-545. *Cell Death Dis*, 10(8): 616.

    https://doi.org/10.1038/s41419-019-1863-z

32. Bachmayr-Heyda A, Reiner AT, Auer K, *et al.*, 2015, Correlation of circular RNA abundance with proliferation--exemplified with colorectal and ovarian cancer, idiopathic lung fibrosis, and normal human tissues. *Sci Rep*, 5: 8057.

    https://doi.org/10.1038/srep08057

33. Yang Z, Xie L, Han L, *et al.*, 2017, Circular RNAs: Regulators of cancer-related signaling pathways and potential diagnostic biomarkers for human cancers. *Theranostics*, 7(12): 3106–3117.

https://doi.org/10.7150/thno.19016

34. Polyak K, 2011, Heterogeneity in breast cancer. *J Clin Invest*, 121(10): 3786–3788.

https://doi.org/10.1172/JCI60534

35. Liu Y, Lu C, Zhou Y, *et al.*, 2018, Circular RNA hsa_circ_0008039 promotes breast cancer cell proliferation and migration by regulating miR-432-5p/E2F3 axis. *Biochem Biophys Res Commun*, 502(3): 358–363.

https://doi.org/10.1016/j.bbrc.2018.05.166

36. Du WW, Fang L, Yang W, *et al.*, 2017, Induction of tumor apoptosis through a circular RNA enhancing Foxo3 activity. *Cell Death Differ*, 24(2): 357–370.

https://doi.org/10.1038/cdd.2016.133

37. Nair AA, Niu N, Tang X, *et al.*, 2016, Circular RNAs and their associations with breast cancer subtypes. *Oncotarget*, 7(49):80967–80979.

https://doi.org/10.18632/oncotarget.13134

38. Du WW, Yang W, Li X, *et al.*, 2018, A circular RNA circ-DNMT1 enhances breast cancer progression by activating autophagy. *Oncogene*, 37(44): 5829–5842.

https://doi.org/10.1038/s41388-018-0369-y

39. Fang L, Du WW, Lyu J, *et al.*, 2018, Enhanced breast cancer progression by mutant p53 is inhibited by the circular RNA circ-Ccnb1. *Cell Death Differ*, 25(12): 2195–2208.

https://doi.org/10.1038/s41418-018-0115-6

40. Xu JZ, Shao CC, Wang XJ, *et al.*, 2019, circTADA2As suppress breast cancer progression and metastasis via targeting miR-203a-3p/SOCS3 axis. *Cell Death Dis*, 10(3): 175.

https://doi.org/10.1038/s41419-019-1382-y

41. Yang R, Xing L, Zheng X, *et al.*, 2019, The circRNA circAGFG1 acts as a sponge of miR-195-5p to promote triple-negative breast cancer progression through regulating CCNE1 expression. *Mol Cancer*, 18(1): 4.

https://doi.org/10.1186/s12943-018-0933-7

42. Siegel RL, Miller KD, Jemal A, 2020, Cancer statistics, 2020. *CA Cancer J Clin*, 70(1): 7–30.

https://doi.org/10.3322/caac.21590

43. Ahmed I, Karedath T, Andrews SS, *et al.*, 2016, Altered expression pattern of circular RNAs in primary and metastatic sites of epithelial ovarian carcinoma. *Oncotarget*, 7(24): 36366–36381.

https://doi.org/10.18632/oncotarget.8917

44. Yang X, Mei J, Wang H, *et al.*, 2020, The emerging roles of circular RNAs in ovarian cancer. *Cancer Cell Int*, 20: 265.

https://doi.org/10.1186/s12935-020-01367-9

45. Ning L, Long B, Zhang W, *et al.*, 2018, Circular RNA profiling reveals circEXOC6B and circN4BP2L2 as novel prognostic biomarkers in epithelial ovarian cancer. *Int J Oncol*, 53(6): 2637–2646.

https://doi.org/10.3892/ijo.2018.4566

46. Chen Q, Zhang J, He Y, *et al.*, 2018, hsa_circ_0061140 Knockdown reverses FOXM1-mediated cell growth and metastasis in ovarian cancer through miR-370 sponge activity. *Mol Ther Nucleic Acids*, 13: 55–63.

https://doi.org/10.1016/j.omtn.2018.08.010

47. Teng F, Xu J, Zhang M, *et al.*, 2019, Comprehensive circular RNA expression profiles and the tumor-suppressive function of circHIPK3 in ovarian cancer. *Int J Biochem Cell Biol*, 112: 8–17.

https://doi.org/10.1016/j.biocel.2019.04.011

48. Torre LA, Bray F, Siegel RL, *et al.*, 2015, Global cancer statistics, 2012. *CA Cancer J Clin*, 65(2): 87–108.

https://doi.org/10.3322/caac.21262

49. Li F, Zhang L, Li W, Deng J, *et al.*, 2015, Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/β-catenin pathway. *Oncotarget*, 6(8): 6001–60013.

https://doi.org/10.18632/oncotarget.3469

50. Li P, Chen S, Chen H, *et al.*, 2015, Using circular RNA as a novel type of biomarker in the screening of gastric cancer. *Clin Chim Acta*, 444: 132–136.

https://doi.org/10.1016/j.cca.2015.02.018

51. Chen S, Li T, Zhao Q, *et al.*, 2017, Using circular RNA hsa_circ_0000190 as a new biomarker in the diagnosis of gastric cancer. *Clin Chim Acta*, 466: 167–171.

https://doi.org/10.1016/j.cca.2017.01.025

52. Li WH, Song YC, Zhang H, *et al.*, 2017, Decreased expression of Hsa_circ_00001649 in gastric cancer and its clinical significance. *Dis Markers*, 2017: 4587698.

https://doi.org/10.1155/2017/4587698

53. Sui W, Shi Z, Xue W, *et al.*, 2017, Circular RNA and gene expression profiles in gastric cancer based on microarray chip technology. *Oncol Rep*, 37(3): 1804–1814.

https://doi.org/10.3892/or.2017.5415

54. Huang G, Zhu H, Shi Y, *et al.*, 2015, cir-ITCH plays an inhibitory role in colorectal cancer by regulating the Wnt/β-catenin pathway. *PLoS One*, 10(6): e0131225.

https://doi.org/10.1371/journal.pone.0131225

55. Wang X, Ren Y, Ma S, *et al.*, 2020, Circular RNA 0060745, a Novel circRNA, promotes colorectal cancer cell proliferation and metastasis through miR-4736 sponging. *Onco Targets Ther*, 13: 1941–1951.

https://doi.org/10.2147/OTT.S240642

56. Zhu CL, Sha X, Wang Y, *et al.*, 2019, Circular RNA hsa_circ_0007142 is upregulated and targets miR-103a-2-5p in colorectal cancer. *J Oncol*, 2019: 9836819.

https://doi.org/10.1155/2019/9836819

57. Zhu M, Xu Y, Chen Y, *et al.*, 2017, Circular BANP, an upregulated circular RNA that modulates cell proliferation in colorectal cancer. *Biomed Pharmacother*, 88: 138–144.

https://doi.org/10.1016/j.biopha.2016.12.097

58. Weng W, Wei Q, Toden S, *et al.*, 2017, Circular RNA ciRS-7-A promising prognostic biomarker and a potential therapeutic target in colorectal cancer. *Clin Cancer Res*, 23(14): 3918–3928.

https://doi.org/10.1158/1078-0432.CCR-16-2541

59. Guo JN, Li J, Zhu CL, *et al.*, 2016, 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*, 9: 7451–7458.

https://doi.org/10.2147/OTT.S123220

60. Zhang P, Zuo Z, Shang W, *et al.*, 2017, Identification of differentially expressed circular RNAs in human colorectal cancer. *Tumour Biol*, 39(3): 1010428317694546.

https://doi.org/10.1177/1010428317694546

61. Qin M, Liu G, Huo X, *et al.*, 2016, Hsa_circ_0001649: A circular RNA and potential novel biomarker for hepatocellular carcinoma. *Cancer Biomark*, 16(1): 161–169.

https://doi.org/10.3233/CBM-150552

62. Yao Z, Luo J, Hu K, *et al.*, 2017, ZKSCAN1 gene and its related circular RNA (circZKSCAN1) both inhibit hepatocellular carcinoma cell growth, migration, and invasion but through different signaling pathways. *Mol Oncol*, 11(4): 422–437.

https://doi.org/10.1002/1878-0261.12045

63. Wang L, Long H, Zheng Q, *et al.*, 2019, Circular RNA circRHOT1 promotes hepatocellular carcinoma progression by initiation of NR2F6 expression. *Mol Cancer*, 18(1): 119.

https://doi.org/10.1186/s12943-019-1046-7

64. Yang J, Li Y, Yu Z, *et al.*, 2020, Circular RNA Circ100084 functions as sponge of miR23a5p to regulate IGF2 expression in hepatocellular carcinoma. *Mol Med Rep*, 21(6): 2395–2404.

https://doi.org/10.3892/mmr.2020.11069

65. Sun XH, Wang YT, Li GF, *et al.*, 2020, Serum-derived three-circRNA signature as a diagnostic biomarker for hepatocellular carcinoma. *Cancer Cell Int*, 20: 226.

https://doi.org/10.1186/s12935-020-01302-y

66. Rybak-Wolf A, Stottmeister C, Glažar P, *et al.*, 2015, Circular RNAs in the mammalian brain are highly abundant, conserved, and dynamically expressed. *Mol Cell*, 58(5): 870–885.

https://doi.org/10.1016/j.molcel.2015.03.027

67. Song X, Zhang N, Han P, *et al.*, 2016, Circular RNA profile in gliomas revealed by identification tool UROBORUS. *Nucleic Acids Res*, 44(9): e87.

https://doi.org/10.1093/nar/gkw075

68. ng P, Qiu Z, Jiang Y, *et al.*, 2016, Silencing of cZNF292 circular RNA suppresses human glioma tube formation via the Wnt/β-catenin signaling pathway. *Oncotarget*, 7(39): 63449–63455.

https://doi.org/10.18632/oncotarget.11523

69. Zhu J, Ye J, Zhang L, *et al.*, 2017, Differential expression of circular RNAs in glioblastoma multiforme and its correlation with prognosis. *Transl Oncol*, 10(2): 271–279.

https://doi.org/10.1016/j.tranon.2016.12.006

70. Zheng J, Liu X, Xue Y, *et al.*, 2017, TTBK2 circular RNA promotes glioma malignancy by regulating miR-217/HNF1β/Derlin-1 pathway. *J Hematol Oncol*, 10(1): 52.

https://doi.org/10.1186/s13045-017-0422-2

71. Chen Z, Duan X, 2018, Hsa_circ_0000177-miR-638-FZD7-Wnt signaling cascade contributes to the malignant behaviors in glioma. *DNA Cell Biol*, 37(9): 791–797.

https://doi.org/10.1089/dna.2018.4294

72. Wang R, Zhang S, Chen X, *et al.*, 2020, EIF4A3-induced circular RNA MMP9 (circMMP9) acts as a sponge of miR-124 and promotes glioblastoma multiforme cell tumorigenesis. *Mol Cancer*, 17(1): 166.

https://doi.org/10.1186/s12943-018-0911-0

73. Liu Y, Ma C, Qin X, *et al.*, 2019, Circular RNA circ_001350 regulates glioma cell proliferation, apoptosis, and metastatic properties by acting as a miRNA sponge. *J Cell Biochem*, 120(9): 15280–15287.

https://doi.org/10.1002/jcb.28795

74. He J, Huang Z, He M, *et al.*, 2020, Circular RNA MAPK4 (circ-MAPK4) inhibits cell apoptosis via MAPK signaling pathway by sponging miR-125a-3p in gliomas. *Mol Cancer*, 19(1): 17.

https://doi.org/10.1186/s12943-019-1120-1

75. Wang J, Zhao L, Shang K, *et al.*, 2020. Long non-coding RNA H19, a novel therapeutic target for pancreatic cancer. *Mol Med,* 26(1): 30.

https://doi.org/10.1186/s10020-020-00156-4

76. Li H, Hao X, Wang H, *et al.*, 2016, Circular RNA expression profile of pancreatic ductal adenocarcinoma revealed by microarray. *Cell Physiol Biochem*, 40(6): 1334–1344.

https://doi.org/10.1159/000453186

77. Yang J, Cong X, Ren M, *et al.*, 2019, 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: 7630894.

https://doi.org/10.1155/2019/7630894

78. Yao J, Zhang C, Chen Y, *et al.*, 2019, Downregulation of circular RNA circ-LDLRAD3 suppresses pancreatic cancer progression through miR-137-3p/PTN axis. *Life Sci*, 239: 116871.

https://doi.org/10.1016/j.lfs.2019.116871

79. Chen YY, Jiang MJ, Tian L, 2020, Analysis of exosomal circRNAs upon irradiation in pancreatic cancer cell repopulation. *BMC Med Genomics*, 13(1): 107.

https://doi.org/10.1186/s12920-020-00756-3

80. Guo X, Zhou Q, Su D, *et al.*, 2020, Circular RNA circBFAR promotes the progression of pancreatic ductal adenocarcinoma via the miR-34b-5p/MET/Akt axis. *Mol Cancer*, 19(1): 83.

https://doi.org/10.1186/s12943-020-01196-4

81. Wong CH, Lou UK, Li Y, *et al.*, 2020, CircFOXK2 promotes growth and metastasis of pancreatic ductal adenocarcinoma by complexing with RNA-binding proteins and sponging MiR-942. *Cancer Res*, 80(11): 2138–2149.

https://doi.org/10.1158/0008-5472.CAN-19-3268

82. Zhang X, Yang D, Wei Y, 2018, Overexpressed CDR1as functions as an oncogene to promote the tumor progression via miR-7 in non-small-cell lung cancer. *Onco Targets Ther*, 11: 3979–3987.

https://doi.org/10.2147/OTT.S158316

83. Wang X, Zhu X, Zhang H, *et al.*, 2018, Increased circular RNA hsa_circ_0012673 acts as a sponge of miR-22 to promote lung adenocarcinoma proliferation. *Biochem Biophys Res Commun*, 496(4): 1069–1075.

https://doi.org/10.1016/j.bbrc.2018.01.126

84. Qu D, Yan B, Xin R, *et al.*, 2018, A novel circular RNA hsa_circ_0020123 exerts oncogenic properties through suppression of miR-144 in non-small cell lung cancer. *Am J Cancer Res*, 8(8): 1387–1402.

85. Xue YB, Ding MQ, Xue L, *et al.*, 2019, CircAGFG1 sponges miR-203 to promote EMT and metastasis of non-small-cell lung cancer by upregulating ZNF281 expression. *Thorac Cancer*, 10(8): 1692–1701.

https://doi.org/10.1111/1759-7714.13131

86. Shangguan H, Feng H, Lv D, *et al.*, 2020, Circular RNA circSLC25A16 contributes to the glycolysis of non-small-cell lung cancer through epigenetic modification. *Cell Death Dis*, 11(6): 437.

https://doi.org/10.1038/s41419-020-2635-5

87. Chen L, Nan A, Zhang N, *et al.*, 2019, Circular RNA 100146 functions as an oncogene through direct binding to miR-361-3p and miR-615-5p in non-small cell lung cancer. *Mol Cancer*, 18(1): 13.

https://doi.org/10.1186/s12943-019-0943-0

88. Li X, Zhang Z, Jiang H, *et al.*, 2018, Circular RNA circPVT1 promotes proliferation and invasion through sponging miR-125b and activating E2F2 signaling in non-small cell lung cancer. *Cell Physiol Biochem*, 51(5): 2324–2340.

https://doi.org/10.1159/000495876

89. Qin S, Zhao Y, Lim G, *et al.*, 2019, Circular RNA PVT1 acts as a competing endogenous RNA for miR-497 in promoting non-small cell lung cancer progression. *Biomed Pharmacother*, 111: 244–250.

https://doi.org/10.1016/j.biopha.2018.12.007

90. Zong L, Sun Q, Zhang H, *et al.*, 2018, Increased expression of circRNA_102231 in lung cancer and its clinical significance. *Biomed Pharmacother*, 102: 639–644.

https://doi.org/10.1016/j.biopha.2018.03.084

91. Hang D, Zhou J, Qin N, *et al.*, 2018, A novel plasma circular RNA circFARSA is a potential biomarker for non-small cell lung cancer. *Cancer Med*, 7(6): 2783–2791.

https://doi.org/10.1002/cam4.1514

92. Huang EY, Chang YJ, Huang SP, *et al.*, 2018, A common regulatory variant in SLC35B4 influences the recurrence and survival of prostate cancer. *J Cell Mol Med*, 22(7): 3661–3670.

https://doi.org/10.1111/jcmm.13649

93. Xia Q, Ding T, Zhang G, *et al.*, 2018, Circular RNA expression profiling identifies prostate cancer-specific circRNAs in prostate cancer. *Cell Physiol Biochem*, 50(5): 1903–1915.

https://doi.org/10.1159/000494870

94. Greene J, Baird AM, Casey O, *et al.*, 2019, Circular RNAs are differentially expressed in prostate cancer and are potentially associated with resistance to enzalutamide. *Sci Rep*, 9(1): 10739.

https://doi.org/10.1038/s41598-019-47189-2

95. Kong Z, Wan X, Lu Y, *et al.*, 2020, Circular RNA circFOXO3 promotes prostate cancer progression through sponging miR-29a-3p. *J Cell Mol Med*, 24(1): 799–813.

https://doi.org/10.1111/jcmm.14791

96. Wu YP, Lin XD, Chen SH, *et al.*, 2020, Identification of prostate cancer-related circular RNA through bioinformatics analysis. *Front Genet*, 11: 892.

https://doi.org/10.3389/fgene.2020.00892

97. Ge S, Sun C, Hu Q, *et al.*, 2020, Differential expression profiles of circRNAs in human prostate cancer based on chip and bioinformatic analysis. *Int J Clin Exp Pathol*, 13(5): 1045–1052.

98. Cai C, Zhi Y, Wang K, *et al.*, 2019, CircHIPK3 overexpression accelerates the proliferation and invasion of prostate cancer

cells through regulating miRNA-338-3p. *Onco Targets Ther*, 12: 3363–3372.

https://doi.org/10.2147/OTT.S196931

99. Wang X, Wang R, Wu Z, *et al.*, 2019, Circular RNA ITCH suppressed prostate cancer progression by increasing HOXB13 expression via spongy miR-17-5p. *Cancer Cell Int*, 19: 328.

https://doi.org/10.1186/s12935-019-0994-8

100. Szymczyk A, Macheta A, Podhorecka M, 2018, Abnormal microRNA expression in the course of hematological malignancies. *Cancer Manag Res*, 10: 4267–4277.

https://doi.org/10.2147/CMAR.S174476

101. Li W, Zhong C, Jiao J, *et al.*, 2017, Characterization of hsa_circ_0004277 as a new biomarker for acute myeloid leukemia via circular RNA profile and bioinformatics analysis. *Int J Mol Sci*, 18(3): 597.

https://doi.org/10.3390/ijms18030597

102. L'Abbate A, Tolomeo D, Cifola I, *et al.*, 2018, MYC-containing amplicons in acute myeloid leukemia: Genomic structures, evolution, and transcriptional consequences. *Leukemia*, 32(10): 2152–2166.

https://doi.org/10.1038/s41375-018-0033-0

103. Liu J, Kong F, Lou S, *et al.*, 2018, Global identification of circular RNAs in chronic myeloid leukemia reveals hsa_circ_0080145 regulates cell proliferation by sponging miR-29b. *Biochem Biophys Res Commun*, 504(4): 660–665.

https://doi.org/10.1016/j.bbrc.2018.08.154

104. Xia L, Wu L, Bao J, *et al.*, 2018, Circular RNA circ-CBFB promotes proliferation and inhibits apoptosis in chronic lymphocytic leukemia through regulating miR-607/FZD3/Wnt/β-catenin pathway. *Biochem Biophys Res Commun*, 503(1): 385–390.

https://doi.org/10.1016/j.bbrc.2018.06.045

105. Dahl M, Daugaard I, Andersen MS, *et al.*, 2018, Enzyme-free digital counting of endogenous circular RNA molecules in B-cell malignancies. *Lab Invest*, 98(12): 1657–1669.

https://doi.org/10.1038/s41374-018-0108-6

106. Mei M, Wang Y, Li Z, *et al.*, 2019, Role of circular RNA in hematological malignancies. *Oncol Lett*, 18(5): 4385–4392.

https://doi.org/10.3892/ol.2019.10836

107. Zhong Z, Lv M, Chen J, 2016, Screening differential circular RNA expression profiles reveals the regulatory role of circTCF25-miR-103a-3p/miR-107-CDK6 pathway in bladder carcinoma. *Sci Rep*, 6: 30919.

https://doi.org/10.1038/srep30919

108. Li P, Liu H, Wang Z, *et al.*, 2016, MicroRNAs in laryngeal cancer: Implications for diagnosis, prognosis and therapy. *Am J Transl Res*, 8(5): 1935–1944.

109. Zhang H, Wang G, Ding C, *et al.*, 2017, Increased circular RNA UBAP2 acts as a sponge of miR-143 to promote osteosarcoma progression. *Oncotarget*, 8(37): 61687–61697.

https://doi.org/10.18632/oncotarget.18671

110. Xiong Y, Zhang J, Song C, 2018, CircRNA ZNF609 functions as a competitive endogenous RNA to regulate FOXP4 expression by sponging miR-138-5p in renal carcinoma. *J Cell Physiol*, 234(7): 10646–10654.

https://doi.org/10.1002/jcp.27744

111. Chen L, Zhang S, Wu J, *et al.*, 2019, circRNA_100290 plays a role in oral cancer by functioning as a sponge of the miR-29 family. *Oncogene*, 36(32): 4551–4561.

https://doi.org/10.1038/onc.2017.89

112. De Rubis G, Krishnan SR, Bebawy M, 2019, Liquid biopsies in cancer diagnosis, monitoring, and prognosis. *Trends Pharmacol Sci*, 40(3): 172–186.

https://doi.org/10.1016/j.tips.2019.01.006

113. Kwapisz D, 2017, The first liquid biopsy test approved. Is it a new era of mutation testing for non-small cell lung cancer? *Ann Transl Med*, 5(3): 46.

https://doi.org/10.21037/atm.2017.01.32

114. Zaporozhchenko IA, Ponomaryova AA, Rykova EY, *et al.*, 2018, The potential of circulating cell-free RNA as a cancer biomarker: Challenges and opportunities. *Expert Rev Mol Diagn*, 18(2): 133–145.

https://doi.org/10.1080/14737159.2018.1425143

115. Lamb YN, Dhillon S, (2017), Epi proColon® 2.0 CE: A blood-based screening test for colorectal cancer. *Mol Diagn Ther*, 21(2): 225–232.

https://doi.org/10.1007/s40291-017-0259-y

116. Baassiri A, Nassar F, Mukherji D, *et al.*, 2020, Exosomal non coding RNA in LIQUID biopsies as a promising biomarker for colorectal cancer. *Int J Mol Sci*, 21(4): 1398.

https://doi.org/10.3390/ijms21041398

117. He AT, Liu J, Li F, *et al.*, 2021, Targeting circular RNAs as a therapeutic approach: Current strategies and challenges. *Signal Transduct Target Ther*, 6(1): 185.

https://doi.org/10.1038/s41392-021-00569-5

118. Wen G, Zhou T, Gu W, 2020, The potential of using blood circular RNA as liquid biopsy biomarker for human diseases. *Protein Cell*, 12(12): 911–946.

https://doi.org/10.1007/s13238-020-00799-3

119. Nsengimana B, Khan FA, Ngowi EE, *et al.*, 2022, Processing body (P-body) and its mediators in cancer. *Mol Cell Biochem*, 477(4): 1217–1238.

https://doi.org/10.1007/s11010-022-04359-7

120. Lampis, A. Ghidini, M. Ratti, *et al.*, 2020, Circulating

tumour DNAs and non-coding RNAs as liquid biopsies for the management of colorectal cancer patients. *Gastrointest Disord*, 2: 212–235.

https://doi.org/10.3390/gidisord2030022

121. Zhang Z, Yang T, Xiao J, 2018, Circular RNAs: Promising biomarkers for human diseases. *EBioMedicine*, 34: 267–274.

https://doi.org/10.1016/j.ebiom.2018.07.036

122. Li Y, Li C, Xu R, *et al.*, 2019, A novel circFMN2 promotes tumor proliferation in CRC by regulating the miR-1182/hTERT signaling pathways. *Clin Sci* (*Lond*), 133(24): 2463–2479.

https://doi.org/10.1042/CS20190715

123. Feng W, Gong H, Wang Y, *et al.*, 2019, circIFT80 Functions as a ceRNA of miR-1236-3p to promote colorectal cancer progression. *Mol Ther Nucleic Acids*, 18: 375–387.

https://doi.org/10.1016/j.omtn.2019.08.024

124. Yin WB, Yan MG, Fang X, *et al.*, 2018, Circulating circular RNA hsa_circ_0001785 acts as a diagnostic biomarker for breast cancer detection. *Clin Chim Acta*, 487: 363–368.

https://doi.org/10.1016/j.cca.2017.10.011

125. Yang C, Wei Y, Yu L, *et al.*, 2019, Identification of altered circular RNA expression in serum exosomes from patients with papillary thyroid carcinoma by high-throughput sequencing. *Med Sci Monit*, 25: 2785–2791.

https://doi.org/10.12659/MSM.915658

126. Fan CM, Wang JP, Tang YY, *et al.*, 2019, circMAN1A2 could serve as a novel serum biomarker for malignant tumors. *Cancer Sci*, 110(7): 2180–2188.

https://doi.org/10.1111/cas.14034

127. Wang X, Yao Y, Jin M, 2020, Circ-0001068 is a novel biomarker for ovarian cancer and inducer of PD1 expression in T cells. *Aging* (*Albany NY*), 12(19):19095-19106.

https://doi.org/10.18632/aging.103706

128. Xu H, Gong Z, Shen Y, *et al.*, 2018, Circular RNA expression in extracellular vesicles isolated from serum of patients with endometrial cancer. *Epigenomics*, 10(2): 187–197.

https://doi.org/10.2217/epi-2017-0109

129. Ji W, Qiu C, Wang M, *et al.*, 2018, Hsa_circ_0001649: A circular RNA and potential novel biomarker for colorectal cancer. *Biochem Biophys Res Commun*, 497(1): 122–126.

https://doi.org/10.1016/j.bbrc.2018.02.036

130. Li XN, Wang ZJ, Ye CX, *et al.*, 2019, Circular RNA circVAPA is upregulated and exerts oncogenic properties by sponging miR-101 in colorectal cancer. *Biomed Pharmacother*, 112: 108611.

https://doi.org/10.1016/j.biopha.2019.108611

131. Li J, Song Y, Wang J, *et al.*, 2020, Plasma circular RNA panel acts as a novel diagnostic biomarker for colorectal cancer detection. *Am J Transl Res*, 12(11): 7395–7403.

132. Pan B, Qin J, Liu X, *et al.*, 2019, Identification of serum exosomal hsa-circ-0004771 as a novel diagnostic biomarker of colorectal cancer. *Front Genet*, 10: 1096.

https://doi.org/10.3389/fgene.2019.01096

133. Huang M, He YR, Liang LC, *et al.*, 2017, Circular RNA hsa_circ_0000745 may serve as a diagnostic marker for gastric cancer. *World J Gastroenterol*, 23(34): 6330–6338.

https://doi.org/10.3748/wjg.v23.i34.6330

134. Li T, Shao Y, Fu L, *et al.*, 2018, Plasma circular RNA profiling of patients with gastric cancer and their droplet digital RT-PCR detection. *J Mol Med* (*Berl*), 96(1): 85–96.

https://doi.org/10.1007/s00109-017-1600-y

135. Sun H, Tang W, Rong D, *et al.*, 2018, Hsa_circ_0000520, a potential new circular RNA biomarker, is involved in gastric carcinoma. *Cancer Biomark*, 21(2): 299–306.

https://doi.org/10.3233/CBM-170379

136. Lu J, Zhang PY, Xie JW, *et al.*, 2019, Hsa_circ_0000467 promotes cancer progression and serves as a diagnostic and prognostic biomarker for gastric cancer. *J Clin Lab Anal*, 33(3): e22726.

https://doi.org/10.1002/jcla.22726

137. Chen X, Chen RX, Wei WS, *et al.*, 2018, PRMT5 circular RNA promotes metastasis of urothelial carcinoma of the bladder through sponging miR-30c to induce epithelial-mesenchymal transition. *Clin Cancer Res*, 24(24): 6319–6330.

https://doi.org/10.1158/1078-0432.CCR-18-1270

138. Shuai M, Hong J, Huang D, *et al.*, 2018, Upregulation of circRNA_0000285 serves as a prognostic biomarker for nasopharyngeal carcinoma and is involved in radiosensitivity. *Oncol Lett*, 16(5): 6495–6501.

https://doi.org/10.3892/ol.2018.9471

139. Hu J, Han Q, Gu Y, *et al.*, 2018, Circular RNA PVT1 expression and its roles in acute lymphoblastic leukemia. *Epigenomics*, 10(6): 723–732.

https://doi.org/10.2217/epi-2017-0142

140. Wu Z, Sun H, Wang C, *et al.*, 2020, Mitochondrial genome-derived circRNA mc-COX_2 functions as an oncogene in chronic lymphocytic leukemia. *Mol Ther Nucleic Acids*, 20: 801–811.

https://doi.org/10.1016/j.omtn.2020.04.017

141. Luo Y, Gui R, 2020, Circulating exosomal CircMYC is associated with recurrence and bortezomib resistance in patients with multiple myeloma. *Turk J Haematol*, 37(4): 248–262.

https://doi.org/10.4274/tjh.galenos.2020.2020.0243

142. Wang Y, Lin Q, Song C, *et al.*, 2020, Circ_0007841 promotes the progression of multiple myeloma through targeting miR-338-3p/BRD4 signaling cascade. *Cancer Cell Int*, 20: 383.

https://doi.org/10.1186/s12935-020-01475-6

143. Li Z, Zhou Y, Yang G, *et al.*, 2019, Using circular RNA SMARCA5 as a potential novel biomarker for hepatocellular carcinoma. *Clin Chim Acta*, 492: 37–44.

https://doi.org/10.1016/j.cca.2019.02.001

144. Zhang H, Deng T, Ge S, *et al.*, 2019, Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7. *Oncogene*, 38(15): 2844–2859.

https://doi.org/10.1038/s41388-018-0619-z

145. Zhang PF, Gao C, Huang XY, *et al.*, 2020, Cancer cell-derived exosomal circUHRF1 induces natural killer cell exhaustion and may cause resistance to anti-PD1 therapy in hepatocellular carcinoma. *Mol Cancer*, 19(1): 110.

https://doi.org/10.1186/s12943-020-01222-5

146. Yang F, Liu DY, Guo JT, *et al.*, 2017, Circular RNA circ-LDLRAD3 as a biomarker in diagnosis of pancreatic cancer. *World J Gastroenterol*, 23(47): 8345–8354.

https://doi.org/10.3748/wjg.v23.i47.8345

147. Zhao SY, Wang J, Ouyang SB, *et al.*, 2018, Salivary circular RNAs Hsa_Circ_0001874 and Hsa_Circ_0001971 as novel biomarkers for the diagnosis of oral squamous cell carcinoma. *Cell Physiol Biochem*, 47(6): 2511–2521.

https://doi.org/10.1159/000491624

148. Zhu K, Niu L, Wang J, *et al.*, 2019, Circular RNA hsa_circ_0000885 levels are increased in tissue and serum samples from patients with osteosarcoma. *Med Sci Monit*, 25: 1499–1505.

https://doi.org/10.12659/MSM.914899

149. Zhu X, Wang X, Wei S, *et al.*, 2017, Hsa_circ_0013958: A circular RNA and potential novel biomarker for lung adenocarcinoma. *FEBS J*, 284(14): 2170–2182.

https://doi.org/10.1111/febs.14132

150. Ayers D, Vandesompele J, 2017, Influence of microRNAs and long non-coding RNAs in cancer chemoresistance. *Genes* (*Basel*), 8(3): 95.

https://doi.org/10.3390/genes8030095

151. Ding C, Yi X, Wu X, *et al.*, 2020, Exosome-mediated transfer of circRNA CircNFIX enhances temozolomide resistance in glioma. *Cancer Lett*, 479: 1–12.

https://doi.org/10.1016/j.canlet.2020.03.002

152. Shao F, Huang M, Meng F, *et al.*, 2018, Circular RNA signature predicts gemcitabine resistance of pancreatic ductal adenocarcinoma. *Front Pharmacol*, 9: 584.

https://doi.org/10.3389/fphar.2018.00584

153. Xia X, Li X, Li F, *et al.*, 2019, A novel tumor suppressor protein encoded by circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent Kinase-1. *Mol Cancer*, 18(1): 131.

https://doi.org/10.1186/s12943-019-1056-5

154. Kartal-Yandim M, Adan-Gokbulut A, Baran Y, 2016, Molecular mechanisms of drug resistance and its reversal in cancer. *Crit Rev Biotechnol*, 36(4): 716–726.

https://doi.org/10.3109/07388551.2015.1015957

155. Zhou R, Wu Y, Wang W, *et al.*, 2018, Circular RNAs (circRNAs) in cancer. *Cancer Lett*, 425: 134–142.

https://doi.org/10.1016/j.canlet.2018.03.035

156. Papatsirou M, Artemaki PI, Scorilas A, *et al.*, 2020, The role of circular RNAs in therapy resistance of patients with solid tumors. *Per Med*, 17(6): 469–490.

https://doi.org/10.2217/pme-2020-0103

157. Kun-Peng Z, Xiao-Long M, Chun-Lin Z, 2018, Overexpressed circPVT1, a potential new circular RNA biomarker, contributes to doxorubicin and cisplatin resistance of osteosarcoma cells by regulating ABCB1. *Int J Biol Sci*, 14(3): 321–330.

https://doi.org/10.7150/ijbs.24360

158. Sang Y, Chen B, Song X, *et al.*, 2019, Circrna_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer. *Mol Ther*, 27(9): 1638–1652.

https://doi.org/10.1016/j.ymthe.2019.05.011

159. Komseli ES, Pateras IS, Krejsgaard T, *et al.*, 2018, A prototypical non-malignant epithelial model to study genome dynamics and concurrently monitor micro-RNAs and proteins *in situ* during oncogene-induced senescence. *BMC Genomics*, 19(1): 37.

https://doi.org/10.1186/s12864-017-4375-1

160. Gokool A, Anwar F, Voineagu I, 2020, The landscape of circular RNA expression in the human brain. *Biol Psychiatry*, 87(3): 294–304.

https://doi.org/10.1016/j.biopsych.2019.07.029

161. Sachs N, Papaspyropoulos A, Ommen DD, *et al.*, 2019, Long-term expanding human airway organoids for disease modeling. *EMBO J*, 38(4): e100300.

https://doi.org/10.15252/embj.2018100300

162. Wiener DJ, Basak O, Asra P, *et al.*, 2018, Establishment and characterization of a canine keratinocyte organoid culture system. *Vet Dermatol*, 29(5): 375–e126.

https://doi.org/10.1111/vde.12541

163. Cao J, Zhang X, Xu P, *et al.*, 2021, Circular RNA circLMO7 acts as a microRNA-30a-3p sponge to promote gastric cancer progression via the WNT2/β-catenin pathway. *J Exp*

Clin Cancer Res, 40(1): 6.

https://doi.org/10.1186/s13046-020-01791-9

164. Zhang X, Wang S, Wang H, *et al.*, 2019, Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression via the AKT1/mTOR pathway. *Mol Cancer*, 18(1): 20.

https://doi.org/10.1186/s12943-018-0935-5

165. Piwecka M, Glažar P, Hernandez-Miranda LR, *et al.*, 2017, Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. *Science*, 357(6357): eaam8526.

https://doi.org/10.1126/science.aam8526

166. Pamudurti NR, Patop IL, Krishnamoorthy A, *et al.*, 2020, An *in vivo* strategy for knockdown of circular RNAs. *Cell Discov*, 6: 52.

https://doi.org/10.1038/s41421-020-0182-y

167. Costa MC, Calderon-Dominguez M, Mangas A, *et al.*, 2021, Circulating circRNA as biomarkers for dilated cardiomyopathy etiology. *J Mol Med* (*Berl*), 99(12): 1711–1725.

https://doi.org/10.1007/s00109-021-02119-6