The functions and clinical significance of circRNAs in hematological malignancies

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Abstract
With covalently closed circular structures, circular RNAs (circRNAs) were once misinterpreted as by-products of mRNA splicing. Being abundant, stable, highly conserved, and tissue-specific, circRNAs are recently identified as a type of regulatory RNAs. CircRNAs bind to certain miRNAs or proteins to participate in gene transcription and translation. Emerging evidence has indicated that the dysregulation of circRNAs is closely linked to the tumorigenesis and treatment response of hematological malignancies. CircRNAs play critical roles in various biological processes, including tumorigenesis, drug resistance, tumor metabolism, autophagy, pyroptosis, and ferroptosis. The N6-methyladenosine modification of circRNAs and discovery of fusion-circRNAs provide novel insights into the functions of circRNAs. Targeting circRNAs in hematological malignancies will be an attractive treatment strategy. In this review, we systematically summarize recent advances toward the novel functions and molecular mechanisms of circRNAs in hematological malignancies, and highlight the potential clinical applications of circRNAs as novel biomarkers and therapeutic targets for future exploration.

Keywords: Circular RNAs, Hematological malignancies, Tumorigenesis, Drug-resistance, Biomarker

Background
Circular RNAs (circRNAs) are a novel type of competing endogenous RNAs (ceRNAs) of the non-coding RNA (ncRNA) families. Without 5′ and 3′ ends, they are hallmarked by covalently closed continuous loops and are more stable than linear RNAs in vivo [1]. CircRNAs are abundant in biological cells, highly conserved, and expressed in a tissue-specific pattern [2]. CircRNAs are classified into four categories, including exon circRNAs (ecRNAs), circular intron RNAs (ciRNAs), exon-intron circRNAs (ElciRNAs), and tRNA intronic circular RNAs (tricRNAs) (Fig. 1). Accumulating evidence has revealed various biological functions of circRNAs, which have attracted widespread attention [3]. Localized in miRNA binding sites, circRNAs could directly sponge miRNAs through miRNA response elements (MREs), thereby negatively regulating the inhibition of target mRNAs [4]. CircRNAs also regulate gene expression and bind to RNA-binding proteins (RBPs), playing critical roles in gene transcription and translation [5, 6]. In addition, the translation potential of circRNAs as protein templates related to tumorigenesis and development has been proved [7]. Since circRNAs are abundant in human peripheral blood and tissues, making them easy to detect [8, 9]. CircRNAs have been illuminated to participate in various biological and physiological processes, containing cell growth, metastasis, stemness, tumor microenvironment, and immune evasion [10, 11], suggesting potential contributions to the pathogenesis of several human diseases.

CircRNAs act as tumor suppressors or oncogenes to participate in the development of a variety of tumors and are becoming novel diagnostic and prognostic biomarkers [12]. The differential expression and function of circRNAs in a variety of cancers have been identified (Fig. 2)
Recently, emerging evidence suggests that circRNAs play vital roles in the tumorigenesis and progression of hematological tumors [14, 15]. Moreover, circRNAs are affective in iron metabolism and N6-methyladenosine (m6A) modification [16, 17]. The artificial circRNAs molecules targeting miRNAs and nanoparticle-based delivery systems provide novel therapeutic prospects [18]. Given that emerging literature has summarized the expression patterns and classical functions of circRNAs in hematological malignancies, here, we focus on the current state of knowledge regarding the novel mechanisms and potential clinical applications of circRNAs among hematological tumors.

Functions of circRNAs in hematological malignancies

Facilitating tumorigenesis of hematological malignancies

Through genome-wide studies of myeloid leukemia, aberrantly expressed circRNAs in acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) were identified [19, 20]. A total of 569 differentially expression circRNAs (DECs) were screened by circRNA microarray
in 6 bone marrow samples from pediatric AML patients, with 273 circRNAs upregulated and 296 downregulated. Functional investigation illustrated that circ-0004136 promoted the proliferation of AML cells by sponging miR-142 [21]. Moreover, circRNA-sequencing of bone marrow samples from AML patients identified the differentially expression of circ_0009910, which promoted the growth of AML cells by downregulating miR-20a-5p [19]. Han et al. found that circ_0001947 curbed cell proliferation by targeting the miR-329-5p/CREBRF axis in AML [22]. Circ_100290, highly expressed in AML, promoted proliferation and restrained apoptosis of AML cells by sponging miR-203 to regulate Rab10 expression [23].

In addition, recent studies have demonstrated that circRNAs could also modulate cell proliferation independent of their related linear RNAs [3]. Circ_0121582, a product of the reverse splicing of GSK3β exon 1 to exon 7, was confirmed to suppress the growth of AML cells [24]. Interestingly, different mechanisms were regulated by circ_0121582 in the cytoplasm and nucleus, respectively. Circ_0121582 formed a sponge with the miR-224/GSK3β axis in the cytoplasm, and bound to the promoter of GSK3β to recruit TET1 in the nucleus [24]. The occurrence of internal tandem duplication (ITD) mutations in the juxtamembrane domain of the FMS-like tyrosine kinase-3 (FLT3) gene (FLT3-ITD) is identified in up to 30% of AML patients, suggesting a significantly worse clinical outcome. Sun et al. reported that circMYBL2 promoted the proliferation of FLT3-ITD-positive AML cells by directly interacting with the RBP PTBP1 in vitro and in vivo [25]. Moreover, knocking down circMYBL2 decreased the phosphorylation of FLT3 kinase in ITD mutant cells, and further weakened the phosphorylation of STAT5, the downstream target of FLT3 critical for AML progression [25]. Another circRNA recently identified in FLT3-ITD-positive AML was circ_0000370, derived from the FLI-1 gene, which was associated with FLT3-ITD. Circ_0000370 facilitated the viability and suppressed apoptosis of FLT3-ITD-positive AML cells by modulation of miR-1299 and S100A7A [26].

In terms of lymphocytic leukemia, knockdown of circPVT1 accelerated the apoptosis of acute lymphocytic
leukemia (ALL) cells by declining the expression of c-Myc and Bcl-2 [27]. Upregulation of circ-0000745 resulted in enhanced proliferation of ALL cells by activating ERK [28]. Transcriptomic sequencing of 21 de novo chronic lymphocytic leukemia (CLL) patients revealed differentially expression of 859 circRNAs distinguished CLL cells from normal B cells [29]. It was recently demonstrated that circ_0132266 participated in CLL tumorigenesis through interacting with miR-337-3p to modulate PML expression [30]. Xia and colleagues demonstrated that circ-CBFB contributed to CLL progression by modulation of the miR-607/FZD3/Wnt/β-catenin cascade [31].

Currently, studies of circRNAs in lymphoma are relative rare, with only some subtypes reported. Ectopic expression of circ-LAMP1 was detected in T-cell lymphoblastic lymphoma (T-LBL) tissues, which promoted T-LBL progression by sponging miR-615-5p and activating DDR2 level [32]. Augmented expression of circ-APC inhibited the growth of diffuse large B-cell lymphoma (DLBCL) cells in vitro and in vivo by recruiting TET1 to the promoter of APC, subsequently resulted in the activation of canonical Wnt/β-catenin signaling pathway [33]. Remarkable overexpression of circ-CDYL was detected in the plasma of mantle cell lymphoma (MCL) and multiple myeloma (MM) patients [34, 35]. Knockdown of circCDYL could inhibit DNA synthesis rate and cell activities to stunt MM progression. Silencing circCDYL decreased the expression of YAP, the key effector of Hippo signaling, and upregulated miR-1180 in MM xenograft model [35, 36]. Circ_0000190, downregulated in the tissues and plasma of MM patients, restrained the proliferation of MM cells through modulating the miR-767-5p/MAPK4 axis [37]. The overexpressed circ_0000142 in MM targeted miR-610 to promote the level of AKT3 mRNA and enhance cell growth, migration and invasion [38]. Moreover, circ_0007841 directly interacted with miR-338-3p to accelerate MM progression [39]. All these results provide evidence that circRNAs mainly function as sponges of miRNAs and form circRNA/miRNA/mRNA axes to participate in the tumorigenesis of hematological cancers (Fig. 3). Nevertheless, further

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**Fig. 3** CircRNA-miRNA-mRNA networks in hematological malignancies. Selected samples of circRNAs and their genomic targets are exhibited for tumor growth, progression and drug resistance. (A) Circ_0000190 was downregulated in MM and inhibited proliferation as well as induced apoptosis of MM cells through negatively regulating the suppression of miR-767-5p to MAPK4, which led to tumor growth. (B) Circ-CBFB, overexpressed in CLL, was identified as a sponge of miR-607 that targeted FZD3. Circ-CBFB promoted FZD3 expression, resulting in activation of the Wnt/β-catenin pathway and consequent progression of CLL. (C) CircPAN3 could inhibit both miR-153-5p and miR-183-5p, thereby upregulating the expression of XIAP. CircPAN3 was also responsible for AML drug resistance via regulating the level of autophagy-associated proteins.
investigations are still needed to explore the detailed mechanism and potential clinical application.

**Participating in drug resistance**
With the clinical application of novel anti-tumor drugs, the efficacy of hematological tumors has been remarkably improved. However, drug resistance is still a bottleneck that hinders better prognosis of patients. CircRNAs are proved to perform pivotal parts in chemoresistance by reducing drug concentration, activating downstream signaling pathways, and modulating DNA repair ability [40, 41]. Li et al. constructed a doxorubicin (ADM)-resistant cell line (HL-60/ADM) and screened differentially expressed ncRNAs using high-throughput sequencing, 1824 circRNAs included. Targets of DECs were enriched in ribonucleoside and purine ribonucleoside triphosphate catabolic process, intracellular, adenyl ribonucleotide binding, and several classical signaling pathways through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, indicating that circRNAs may participate in drug resistance in AML via modulating multiple biological processes [42]. Moreover, circPAN3 was validated to mediate ADM-resistance of AML cells via targeting the miR-153-5p/miR-183-5p/XIAP axis as well as enhancing autophagy activity, and to promote the expression of apoptosis-marked proteins [14, 43]. Knockdown of circMYBL2 accelerated apoptosis and inhibited proliferation of AML cells resistant to quizartinib, a selective and efficient FLT3 inhibitor, indicating circMYBL2 inducing quizartinib resistance in AML [25].

The application of tyrosine kinase inhibitors (TKIs), represented by imatinib (IM), has doubled the 5-year overall survival (OS) of CML patients [44]. Nevertheless, TKI resistance is gradually being common in clinical practice. Several studies have demonstrated the participation of circRNAs in drug resistance of CML cells. Knocking down circ_0080145 in IM-resistant CML cell lines (K562/IM, KU812/IM) suppressed the glycosylation process and cell growth and induced apoptosis through circ_0080145/miR-326/PPIA1 axis [15]. Besides, the expression of circBA9.3 was positively related to the BCR-ABL level among TKI-resistant CML patients. Mechanistically, circBA9.3 strengthened the antiapoptotic properties of K562 cells and upregulated the levels of both ABL1 and BCR-ABL1 proteins to reduce the sensitivity of leukemia cells to TKIs, thereby promoting resistance against TKI therapy [45]. Circ_100053 was overexpressed in IM-resistant CML patients and K562/IM cells and was associated with advanced clinical stages and the mutation status of BCR-ABL, indicating the contribution to IM resistance of CML, nevertheless, with the unclear mechanism [46]. As a miR-34a-5p sponge, circ_0009910 could promote cell proliferation, block apoptosis in K562/R cells, and activate ULK1-induced autophagy, leading to increased resistance of CML cells to IM [47].

As sponges of different miRNAs, circRNAs may participate in different mechanisms to induce drug resistance in the same disease. Circ_0007841 was involved in the bortezomib (BTZ) tolerance [48] and ADM-resistance in MM cells, and induced chemoresistance by activating ABCG2 [49]. Taken together, circRNAs mediate chemoresistance by regulating signaling transduction pathways or forming ceRNA regulatory networks, and may act as novel therapeutic targets to improve the efficacy of refractory/relapsed patients.

**Regulation of tumor metabolism**
Represented by glycolysis, fatty acid oxidation, and amino acid metabolism, metabolic reprogramming is a typical hallmark in cancer cells [50]. Tumor cells are featured by the strong dependence on glycolysis to provide energy despite sufficient oxygen availability [51]. Targeting glycolysis has been revealed to be a promising therapeutic strategy for hematological malignancies [52]. Hexokinase-2 (HK2) and glucose transporters (GLUT) act as critical modulators of glycolysis progress [53]. A recent study confirmed that silencing circ_0080145 suppressed the glucose consumption, lactic acid content, and the HK2 levels in IM-resistant CML cell lines, indicating the regulatory effect of circ_0080145 on glycolysis in IM-resistance [15]. Aberrant high expression of circ_100290 upregulated GLUT1 by targeting miR-378a to promote the glycolysis in oral squamous cell carcinoma (OSCC) cells [54]. Circ_100290 was also overexpressed in AML, co-expressed with Rab10 [23]. As a target of miR-432-5p, Rab10 participated in the decreased glycolysis induced by miR-432-5p in glioma [55]. Knockdown of circ-PVT1 reduced the glycolytic metabolism of OSCC cells by targeting the miR-106a-5p/HK2 axis [56]. Although circ-PVT1 has been found to be involved in the occurrence of ALL, its regulation on the glucose metabolism of hematological malignancies has not yet been reported. In addition, further investigations on the specific function of circRNAs and glycolysis in hematological tumors are warranted.

Increased de novo synthesis of fatty acids and fat accumulation present in diverse tumors are responsible for tumor development [57]. The content of lipoproteins is tightly connected with the phenotypic and clinical characteristics of hematological malignancies [58]. Recent studies have clarified that circRNAs maintained the global adipocyte transcriptional program of lipid biosynthesis and metabolism [59]. Moreover, circFASN enhanced the promotion of tacrolimus on triglyceride
accumulation [60]. Nevertheless, the mechanism of circRNAs in lipid metabolism of malignancies is still unclear, which is expected to become a novel field in the study of circRNAs in hematological tumors.

**Novel functions of circRNAs**

**Inducing autophagy**

Autophagy is a primary intracellular degradation process regulating tumorigenesis and associated with the sensitivity of tumor cells to chemotherapeutic drugs [61]. Emerging discoveries indicated that circRNAs played significant roles in tumor autophagy [62]. Enhanced autophagic activity was found in ADM-resistant AML cell lines, THP1/ADM and K562/ADM. Silencing circPAN3 reduced the levels of autophagy markers, including the LC3-II/LC3I ratio and Beclin-1. The targeted miRNAs of circPAN3, analyzed by target prediction database, were related to AMPK signaling pathway and downregulated in THP-1 cells with circPAN3 overexpression. Taken together, circPAN3 may activate MAPK pathway to enhance autophagy to induce chemo-resistance in AML [14].

Silencing circ_0009910 resulted in downregulation of ULK1, an autophagy promoter overexpressed in IM-resistant K562 cells. It was further confirmed that circ_0009910 could activate ULK1-induced autophagy via sponging miR-34a-5p, thereby promoting the IM resistance of CML cells [47]. CircCDYL was demonstrated to enhance the autophagic level in breast cancer through miR-1275/ATG7/ULK1 axis [63]. It is worth noting that upregulated levels of circCDYL were also detected in MCL and MM and might serve as potential biomarkers for diagnosis [34, 35]. However, the involvement of circCDYL in the autophagy of hematological malignancies still needs further investigation. Although investigations on circRNAs in tumor autophagy are still in infancy, it will bring new opportunities for future diagnosis and treatment of hematological malignancies.

**Regulating pyroptosis**

Pyroptosis is an inflammasome-activated programmed cell death pathway, characterized by the immediate formation of pores in cell membrane and increased permeability [64]. Induction of pyroptosis represents a novel potential therapeutic strategy for hematological malignancies [65]. The latest studies have illuminated the regulation of circRNAs on pyroptosis in human diseases. CircACTR2, upregulated in high-glucose-treated HK-2 cells, was proved to increase pyroptosis by evaluating propidium iodide (PI) uptake and lactate dehydrogenase (LDH) level [66]. Besides, circ_0076631, overexpressed in glucose-stressed cardiomyocytes and serum of diabetic patients, was validated to activate pyroptosis via circ_0076631/miR-214-3p/caspase-1 axis in diabetic cardiomyopathy [67]. High-throughput sequencing analysis showed the high expression of miR-214-3p in primary cutaneous follicle center lymphoma (PCFCL), suggesting the potential of circRNA/miRNA axis in pyroptosis of lymphoma [68]. The participation of circHIPK3 in pyroptosis was recently reported. CircHIPK3 could downregulate miR-421, leading to the increased FOXO3a expression, thereby inhibiting pyroptosis and releasing IL-1β and IL-18 [69]. Previous studies have found that the high expression of circHIPK3 in CML was significantly associated with poor prognosis [70]. Besides, AKT/FOXO3a pathway was involved in the apoptosis of AML [71]. Genetic polymorphisms of IL-18 and IL-1β were confirmed related to the prognosis of AML [72]. However, whether circHIPK3 could influence the pyroptosis level in leukemia remains further investigations. Overall, the regulation of circRNAs on pyroptosis is a hopeful therapeutic target, but its role in hematological malignancies is yet to be fully understood.

**Function of circRNAs in ferroptosis**

Different from autophagy and apoptosis, ferroptosis is an iron- and reactive oxygen species (ROS)-dependent form of programmed cell death activated by iron oxidation [73, 74]. Accumulating studies have reported the regulatory mechanisms of ncRNAs in ferroptosis of tumors, but few of them focused on circRNAs [75]. Xu et al. reported that circIL4R accelerated tumorigenesis and refrained ferroptosis by regulating the miR-761/ITGB8 axis [77]. GPX4, a key regulator of ferroptosis, was overexpressed in primary MM cells [78]. However, both the circRNA/miRNA/GPX4 axis and its function in ferroptosis in MM have not been revealed. Although the relationship between circRNAs and ferroptosis in hematological malignancies has not been reported before, emerging evidence suggests that the changes in iron metabolism are central characters of leukemia [79]. Typhaneoside (TYP) was proved to prevent AML progression through triggering autophagy and ferroptosis. Therefore, targeting iron metabolism, such as ferroptosis, is likely to provide promising therapeutic options for individualized treatment of leukemia.

**circRNAs and m6A modification**

m6A methylation has emerged recently as the novel mechanism of RNA modification, which executes important functions in malignant hematopoiesis, including AML [80]. The interplay between m6A modification and circRNAs provides novel insights into the therapeutic strategy of malignancies [81, 82]. Zhou et al.
demonstrated that the written and read complexes of m^A modification in circRNAs were the same as those of mRNAs, but the modification patterns were distinct [83]. A growing body of evidence indicates that m^A modification could modulate the production and function of circRNAs. The m^A circRNAs expressed in a cell-type-specific pattern, indicating that m^A modification of circRNAs may exert different biological functions in different cell types [83, 84].

m^A modification of circRNA inhibits innate immunity by blocking RIG-I activation. Moreover, the m^A reader YTHDF2 could bind to m^A-circRNA, thereby suppressing the innate immunity [17]. Chen et al. identified that circNSUN2 could form a circNSUN2/IGF2BP2/HMGA2 RNA-protein ternary complex to enhance the stability of HMGA2 mRNA in colorectal carcinoma [85]. Microarray analysis of DECs in poorly differentiated gastric adenocarcinoma revealed that most DECs had m^A modification, and the trend of m^A modification changes was consistent with the expression level of circRNAs [86]. Circ_0001105 suppressed the progression of osteosarcoma through sponging miR-766 to enhance the expression of YTHDF2 [87]. Interestingly, the inhibition of YTHDF2 selectively targeted leukemic stem cells (LSCs) in AML, indicating the potential functions of circRNA regulated YTHDF2 in the progression of AML [88]. In addition, circ_KLAA1429 could promote the progression of HCC by regulating the m^A-YTHDF3-Zeb1 axis. It was confirmed that SNHG14/miR-5590-3p/Zeb1 axis enhanced the progression and immune evasion through regulating PD-1/PD-L1 checkpoint in DLBCL, which provide an innovative perspective for circRNA mediated immunotherapy of lymphoma [90]. Nevertheless, the m^A modification of circRNAs in hematological malignancies has rarely been reported yet. Further studies on how m^A modification modulates the production and function of circRNAs in hematological malignancies will improve our understanding of the biological function of circRNAs.

**Function of fusion circRNAs**

Gene fusion is a central class of somatic mutational events in hematological malignancies through chromosomal rearrangements triggered by DNA double-strand breaks. As high-risk factors of AML, cytogenetic abnormalities are featured by fusion proteins, including AML1-ETO, PML-RARα, and MLL-AF9, originated from chromosomal translocations, which have been acknowledged as specific biomarkers for prognosis [91]. Additionally, translocations produce not only fusion mRNAs but also fusion circRNAs (f-circRNAs) [92]. Despite the lack of specific mechanisms, f-circRNAs are oncogenic in in vitro and in vivo models [93]. Human mixed lineage leukemia (MLL) gene is involved in chromosome translocations with a multitude of partners, such as AF9 (MLLT3) [94]. Several f-circRNAs have been identified from MLL fusion genes, including MLL-AF9, MLL-AF4, and MLL-ENL [95]. The MLL-AF9 fusion gene is predominantly expressed in AML. Sanger sequencing revealed the existence of f-circM9_1 and f-circM9_2 in THP1 cells. F-circM9 overexpression suppressed apoptosis induced by cytarabine (Ara-C) and arsenic trioxide (ATO) in K562 cells. Moreover, the spleens of mice transplanted with f-circM9 overexpressed leukemia cells were relatively bigger with more leukemia cells, and decreased apoptosis in bone marrow when treated with Ara-C [93]. AF4 is another partner of MLL fusion genes. Four f-circRNAs were detected from AF4 gene, including circAF4 (EX3-4), circAF4 (EX3-5), circAF4 (EX5-6), and circAF4 (EX12). CircAF4 was upregulated in leukemia patients and cells with MLL-AF4 translocation. CircAF4 enhanced proliferation and blocked apoptosis through circAF4/miR-128-3p/MLL-AF4 axis. Knockdown of circAF4 extended survival times of mice [96].

**Potential clinical application of circRNAs**

**Promising biomarkers for diagnosis and prognosis**

CircRNAs are widely and conservatively expressed in hematopoietic cells [97]. As a result of their abundance and accessibility, circRNAs are expected to be ideal biomarkers in the diagnosis and prognosis of hematological malignancies. Among all the circRNAs, PVT1 has been considered to participate in the pathogenesis of hematological malignancies [98, 99]. CircPVT1 showed increased expression in ALL, pediatric B-precursor ALL and AML cases harboring MYC amplifications in the form of dmin, hsr, or ring chromosomes (AML-Amp) [27, 100, 101]. Silencing circPVT1 was validated to inhibit cell proliferation and induce apoptosis in ALL [27]. Additionally, circPVT1 was overexpressed in AML-Amp cases leading to the identification between various karyotypes of AML [101].

Due to the high heterogeneity of hematological malignancies and the cell-type specificity of circRNAs, there are specific expressions of circRNA in different types of hematological diseases (Table 1). At present, a variety of circRNAs have performed promising function for evaluating prognostic model, such as circ_0003602, circ_0005571, circ_0074371, circ_0007609, circ_0012152, hsa_circ_0001857 and circ_001247 [102, 103]. Circ-Foxo3, Circ-RPS6KB1, circ-CSMD2, circ-ANXA2, circ-PWP2, circ-RBM5, circ-ZZEF1, circ-GSK3B and circ-FOXP1 could potentially identify AML patients from healthy groups [104, 105]. Among them, circ-ANXA2 overexpression was related to shorter event-free survival (EFS) and OS of AML patients. Meanwhile, AML
### Table 1  Circular RNAs implicated in hematological malignancies

| Disease | CircRNA | Expression | Phenotype | Clinical significance | Possible target/mechanism | Ref. |
|---------|---------|------------|-----------|-----------------------|----------------------------|------|
| AML     | circRNA-DLEU2 | Up | proliferation (+,), apoptosis (−), tumor formation (+) | / | miR-496/PRKACB | [125] |
| CIRC_100290 | Up | proliferation (+,), apoptosis (−) | / | miR-203/Rab10 | [23] |
| circPAN3 | Up | autophagy (+), apoptosis (−), ADM-resistance (+) | / | miR-153-5p/miR-183-5p/XIAP | [14, 43] |
| circ-ANXA2 | Up | proliferation (+), apoptosis (−) | high disease risk, poor risk stratification, low CR level, short EFS and OS | miR-23a-5p/miR-503-3p | [105] |
| circ_100290 | Up | proliferation (+,), apoptosis (−) | / | miR-203/Rab10 | [23] |
| circ_0009910 | Up | proliferation (+,), apoptosis (−), cell cycle (+) | FLT3-ITD+ | miR-153-5p/miR-183-5p/XIAP | [14, 43] |
| circMYBL2 | Up | proliferation (+), quizartinib resistance (+) | FLT3-ITD+ | PTBP1, FLT3 kinase translational (+) | [25] |
| cinc-0004136 | Up | proliferation (+) | / | miR-142 | [21] |
| circ-HIPK2 | Down | differentiation (+) | ATRA-induced differentiation | miR-1299/S100A7A | [26] |
| circ_001947 | Down | proliferation (−), apoptosis (+) | white blood cell, hemoglobin, diagnosis, prognosis | miR-329-5p/CREBRF | [22] |
| circ_0121582 | Down | proliferation (−) | / | miR-224/GSK3β, TET1/GSK3β/Wnt/β-catenin | [31] |
| CML     | circ_0080145 | Up | proliferation (+) | / | miR-2-9k | [20] |
| CIRC_0009910 | Up | proliferation (+,), autophagy (+,), apoptosis (−) | imatinib resistance, short OS | miR-34a-5p/UKL1 | [47] |
| circBA9.3 | Up | proliferation (+,), apoptosis (−) | TKI-resistance | c-ABL1 & BCR-ABL1 level (+) | [45] |
| circ_100053 | Up | / | distribution of WBC count, FAB subtypes, short OS and LFS | / | [106] |
| circ_0080145 | Up | proliferation (+,), glycolysis (+,), apoptosis (−) | IM-resistance | miR-326/PPFIA1 | [15] |
| ALL     | circPVT1 | Up | proliferation (+,), apoptosis (−) | / | miR-128-3p/MLL-AF4 | [96] |
| circAF4 | Up | apoptosis (−), leukemogenesis (+) | risk stratification | c-Myc & Bcl-2 expression (+) | [27] |
| CLL     | circ-CBF8 | Up | progression (+,), apoptosis (−) | diagnosis, low survival time, independent predictor of prognosis | miR-607/FZD3/Wnt/β-catenin pathway | [31] |
| circ-RPL15 | Up | proliferation (+) | IGHV mutation status | miR-146b-3p/RAS/RAF1/MEK/ERK pathway | [108] |
| circ_0132266 | Down | proliferation (−), apoptosis (−) | / | miR-337-3p/PML | [30] |
| circ-APC | Down | proliferation (−), cell cycle (−) | Ann Arbor stage, CHOP-like and rituximab resistance, short OS, independent prognostic factor | miR-888/APC, TET1/APC, inactivate Wnt/β-catenin pathway | [33] |
| MCL     | circCDYL | Up | proliferation (+) | diagnosis | miR-615-5p/DDR2 | [32] |
| T-LBL   | circ-LAMP1 | Up | proliferation (+,), apoptosis (−) | / | ABCG2 level (+) | [49] |
| MM      | circ_0007841 | Up | proliferation (+) | clinical type, cytogenetic mutation, bone destruction, R-ISS staging, DOX resistance | miR-1180/YAP | [35] |
| circCDYL | Up | DNA synthesis (+,), apoptosis (−) | ISS and DS stage, diagnosis, short OS | miR-1180/YAP | [35] |
| circ_0000190 | Down | proliferation (−), apoptosis (−), tumor growth (−) | ISS and DS stage, high risk, short PFS, OS | miR-767-5p/MAPK pathway | [37] |
| circ-SMARC5 | Down | proliferation (−), apoptosis (−) | β2-MG level, ISS stage, short PFS and OS | miR-767-5p | [126] |

Note: (+) means promotion and (−) means suppression
patients achieved complete remission (CR) presented lower level of circ-ANAX2 than those did not reach CR, accompanied by longer EFS and OS [105]. Receiver operating characteristic (ROC) curve analysis revealed that the expression of circ-VIM could distinguish AML patients from healthy groups. Highly expressed circ-VIM acted as an independent prognostic factor for OS and leukemia-free survival (LFS) in AML [106]. Interestingly, the expression level of the same circRNA differs in subtypes of the same disease, highlighting the specificity of circRNAs as biomarkers. Circ_0075001 was overexpressed in M0 or M1 subtype of AML patients and significantly downregulated in M2, M4 and M5 subgroups, showing the potential to distinguish the differentiation degree of the AML [107].

The high expression of circHIPK3 in serum of CML patients was related to Sokal relative risk, an independent factor of CML prognosis, and shorter OS, indicating poor clinical outcome [70]. The level of circ-RPL15 was negatively correlated to the mutation state of immunoglobulin heavy chain (IGHV) gene, predicting poorer OS [108]. In DLBCL, downregulating plasma circ-APC presented diagnostic potential and was related to advanced Ann Arbor stage, low International Prognostic Index, rituximab resistance, and shorter OS [33]. The high expression of circRNA_101237 was associated with shorter OS and PFS in MM patients [109]. What is more, the expression of circRNAs in several diseases exhibited temporal specificity, which indicated that circRNAs were likely to predict clinical outcome [110]. A total of 508 circRNAs expressed dynamically throughout the treatment of all-trans retinoic acid (ATRA) in NB4 cells, and independently from the parent genes [111]. The low expression state of circ_0004277 in AML patients was diminished after chemotherapy, while the level of circ_0004277 decreased again when patients relapsed after CR, demonstrating the relationship between the increasing expression and good curative effect [112]. As consequence, the expression of circRNAs is dynamic during disease progression, which provides new aspects for therapeutic efficacy and prognosis evaluation.

The existing modalities of disease diagnosis and efficacy evaluation are invasive. Liquid biopsy, being non-invasive and repeatable, is becoming a new diagnostic tool. Accumulating evidence discovers the enrichment of circRNAs in exosomes. Exosomes protect inner circRNAs from influences of extracellular substances, making it more possible for detecting the existence of exosomal circRNAs [113]. Exosomal circRNAs act a significant part mainly in proliferation and tumor metastasis [114]. Mc-COX2, a mitochondrial genome-derived circRNA, was significantly enriched in exosomes of plasma from CLL patients, and was positively correlated with worse OS [115]. Associated with deletion 17p, t (4; 14), Durie-Salmon staging and international staging system, the level of exosomal circMYC was higher in bortezomib-resistant patients than non-resistant groups [116]. Additionally, the exosomal circ_0007841 was validated to enhance proliferation and metastasis and suppress apoptosis via activating PI3K/AKT pathway in MM cell lines [39]. Although a large number of circRNAs with biomarker value have been discovered by high-throughput sequencing, the targets and mechanisms are still unclear. The constantly emerging circRNA databases provide great convenience for target prediction and expression visualization. Here, we summarize 10 representative circRNA databases (Table 2).

circRNA-related therapeutic strategies

The circRNA-miRNA-mRNA axis has become a vital mechanism in hematological tumorigenesis. As circRNAs contain multiple miRNA binding sites, targeted inhibition of circRNAs exerts more therapeutic advantages and potential than targeted inhibition of single miRNA/gene. RNA interference (RNAi) is one of the most common methods to determine the function of circRNA through loss-of-function approach. Transcripts of circRNAs could be packaged into viral vectors or oligonucleotide and then delivered to target cells to mediate their therapeutic effects [96]. Inhibiting the expression of specific circRNA could enhance the protective function of the relevant miRNAs in inhibiting oncogenes, such as XIAP, β-catenin, GSK3β and YAP [24, 31, 35, 43]. Recently, the CRISPR/Cas9-mediated genetic engineering technology provides a robust tool for circRNAs investigation. The CRISPR/Cas-assisted homologous recombination method can replace circRNA gene with a marker gene, thereby consuming circRNAs without affecting the existing gene [117]. Future investigations fueled by the well-defined guide RNA (gRNA) libraries designed for circRNA will promote the targeted therapy based on circRNA screening.

At present, a practical artificial circRNA sponge could be synthesized using simple enzymatic ligation approach. The artificial circRNA molecule is applied as an exogenous miRNA inhibitor to effectively bind and block mature miRNA, providing a promising strategy for cancer therapy [18]. Jost et al. engineered the artificial circRNA sponges into customized miRNA to isolate miR-122 from hepatitis C virus (HCV). In addition, circRNAs can also be used as protein sponges, and the binding sites obtained from SELEX or CLIP data can be used for many RBPs [118]. The anti-HCV circular miRNA-122 RNA sponge can be used in combination with the sequence of host factors necessary to isolate the propagation of HCV, such as hnRNPL and HuR [118]. Therefore, the artificial
circRNA sponge is a promising tool in circRNA-based anti-tumor therapy, which has potential value in clinical application. In addition, emerging evidence indicated the potential therapeutic value of tumor-related functional peptides encoded by circRNAs, especially cancer-inhibiting peptides/proteins, such as β-catenin-370aa encoded by circβ-catenin, circPPP1R12A-73aa by circPPP1R12A, and AKT3-174aa by circ-AKT3 [119]. These functional peptides can play important roles in tumorigenesis, which made them potential novel targets for drug development [119]. Due to the potential development value and clinical utility of functional peptides encoded by circRNAs, the functional peptides may be used in the research and treatment of hematological malignancies in the future.

Both the artificial circRNA and functional peptides need to be transported to the cell through an appropriate delivery system. Nanoparticles could be used to treat tumor in a variety of ways, such as intravenous injection and tail vein injection, and have become promising tools for cancer treatment. Recently, Wang et al. established a new plasmid delivery system, Micropoly-transfecter, which can deliver circ-1073 plasmid through intratumoral injection, thereby inhibiting tumor progression [120]. Moreover, accumulating evidence has indicated the potential value of exosomal circRNAs in clinical application [121]. Exosomes could carry circ-0051443 from normal cells to HCC cells, and inhibit the malignant biological behaviors through inducing apoptosis and cell cycle arrest [122].

CircRNAs play vital roles in the tumor microenvironment (TME) by regulating the immune surveillance and remodeling the extracellular matrix [9, 123]. CircRNA-002178 was indicated to promote the expression of PD-L1 in tumor cells through the ceRNA mechanism. Meanwhile, circRNA-002178 in tumor cells was delivered from exosomes to CD8+ T cells to achieve immune evasion of tumor cells by promoting PD-1 expression [124]. The regulation of PDL-1/PD-1 pathway by circRNA-002178 may also provide a new direction for the development of tumor-targeted drugs. Currently, the circRNA-based targeted therapy in hematological malignancies is still in its infancy. Therefore, regulation of PD-1/PD-L1 by targeting relevant circRNA may be a promising direction of future immune therapy.

**Conclusion and future perspectives**

Emerging studies have revealed that the expression of circRNAs is strongly associated with tumorigenesis and prognosis of hematological malignancies. However, most of them were limited in the abnormal expression and ceRNA functions, rarely in clinical significance. Due to the convenience of circRNAs detection form peripheral blood, circRNAs may act as ideal biomarkers with the potential of clinical application. The expression of circRNAs is dynamic throughout the whole process of chemotherapy, suggesting that detecting the level of circRNAs may reflect the disease status in real time, so as to estimate the therapeutic efficacy in time. Nevertheless, such biomarkers are not specific enough for clinical appliance, which could constitute one of the focuses for future study. Current studies have confirmed that circRNAs regulate cell activity and tumor growth mainly by sponging to miRNAs and RBPs.

### Table 2 CircRNA databases

| Name               | Website address                        | Description                                                                 | Ref.   |
|--------------------|----------------------------------------|------------------------------------------------------------------------------|--------|
| circBase           | https://circbase.org/                  | A public dataset of thousands of circRNAs in eukaryotic cells                | [127]  |
| circInteractome    | https://circinteractome.nia.nih.gov/   | A computational tool enabling the prediction and mapping of binding sites for RBPs and miRNAs on reported circRNAs | [128]  |
| CIRCpedia V2       | https://www.picb.ac.cn/rnomics/circpedia/ | An updated comprehensive database containing circRNA annotations from over 180 RNA-seq datasets across six different species | [129]  |
| circRNAAdb         | https://reprod.njmu.cn/cgi-bin/circRNAdb/circRNAAdb.php | A comprehensive database of circular RNA molecules in humans                  | [130]  |
| CSCD               | https://gb.whu.edu.cn/CSCD             | An integrated interactional database of cancer-specific circRNAs              | [131]  |
| exoRBase           | https://www.exoRBase.org               | A repository of circRNA, IncRNA and mRNA derived from RNA-seq data analyses of human blood exosomes | [132]  |
| MiOncoCirc         | https://mioncocirc.githubusercontent.io/| A compendium of circular RNAs compiled from cancer clinical samples          | [133]  |
| CircAtlas 2.0      | https://circatlas.biols.ac.cn/         | A database of over one million of circRNAs across 6 species (human, macaca, mouse, rat, pig, chicken) and tissues | [134]  |
| CircBank           | https://www.circbank.cn/index.html     | A comprehensive database of human circRNA including more than 140,000 human annotated circRNA from different source | [135]  |
| NoncoRNA           | https://www.ncdtcdb.cn:8080/NoncoRNA/  | A database for experimentally supported ncRNA and drug target associations in cancer | [136]  |
The development of bioinformatics technology has greatly promoted the investigation of circRNA-miRNA axis. However, the specific content and mechanism of ceRNA network in hematological malignancies are still unclear. There remain a large number of circRNAs with unknown functions, and the involved mechanism is yet to be validated. Whether circRNAs participate in hematological cancers through other manners such as encoding peptides needs further investigation.

In this review, we not only summarize the contributions of circRNAs to the pathogenesis, diagnosis, chemo-resistance, and prognosis of hematological malignancies, but also put up novel biological functions and perspectives for the future clinical significances of circRNAs as therapeutic targets as well as novel treatment strategies. CircRNAs have great potential in targeted therapy due to its known regulatory functions, and the stability of circRNAs may be conducive to identify hematological malignancies by body fluids. Nevertheless, the mechanism involved in the interaction between circRNAs and hematological tumors is not fully understood yet. What’s more, although it is confirmed that circRNAs can act as potential diagnosis and prognosis biomarkers, most of the available circRNA-biomarkers are still not specific and sensitive enough to apply in clinical practice. Further studies on large-cohort prospective clinical trials will verify and promote the clinical application of circRNA biomarker candidates. Irrespective of these defects, circRNAs may still be utilized for targeted therapy in the future.

Abbreviations

circRNA: Circular RNA; ceRNA: Competing endogenous RNA; ncRNA: Non-coding RNA; eRNA: Exon circRNA; ciRNA: Circular intron RNA; EcIRNA: Exon-intron circRNA; trcRNA: TRNA intronic circular RNA; MRE: miRNA response element; RBP: RNA-binding protein; m^6^A: N6-methyladenosine; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; DEC: Differentially expression circRNA; MLL: Mixed lineage leukemia; FLT3: FMS-like tyrosine kinase-3; ALL: Acute lymphocytic leukemia; CLL: Chronic lymphocytic leukemia; T-LL: T-cell lymphoblastic lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle cell lymphoma; MM: Multiple myeloma; ADM: Doxorubicin; GO: Gene ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; TKI: Tyrosine kinase inhibitor; OS: Overall survival; BTZ: Bortezomib; HK2: Hexokinase-2; GLUT: Glucose transporters; OSCC: Oral squamous cell carcinoma; PI: Propidium iodide; LDH: Lactate dehydrogenase; PFCCL: Primary cutaneous follicle center lymphoma; ROS: Reactive oxygen species; TYP: Typhaneoside; LSC: Leukemic stem cell; s-circRNA: Fusion circRNA; MLL: Mixed Lineage Leukemia; Ara-C: Cytarabine; ATO: Arsenic trioxide; AML-Amp: AML cases harboring MYC amplifications in the form of dmin, hsr, or ring chromosomes; EFS: Event-free survival; CR: Complete remission; ROC: Receiver operating characteristic; LFS: Leukemia-free survival; GIVH: Immunoglobulin heavy chain; NHL: Non-Hodgkin lymphoma; ATRA: All-trans retinoic acid; RNAi: RNA interference; gRNA: Guide RNA; HCV: Hepatitis C virus; TME: Tumor microenvironment.

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Authors' contributions

X.Z. and L.Z. wrote and edited this manuscript and created figures and tables. X.Z., X.W. and K.H. reviewed and revised the manuscript. X.W. provided direction and guidance throughout the preparation of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Competing interests

The authors declare that they have no competing interests.

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References

1. Jeck WR, Sorrentino JA, Wang K, Stevin MK, Burd CE, Liu J, Marzluff WF, Sharpless NE. Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA. 2013;19:141–57.
2. Zhang Q, Wang W, Zhou Q, Chen C, Yuan W, Liu J, Li X, Sun Z. Roles of circRNAs in the tumour microenvironment. Mol Cancer. 2020;19:14.
3. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Mol Cell Biol. 2020;21:1475–90.
4. Shen T, Han M, Wei G, Ni T. An intriguing RNA species—perspectives of circularized RNA. Protein Cell. 2015;6:871–80.
5. Yang ZG, Awam FM, Wu WW, Zeng Y, Liu J, Wu D, Gupta S, Yang W, Yang BB. The circular RNA interacts with STAT3, increasing its nuclear translocation and wound repair by modulating Dnmt3a and mIrin-17 function. Mol Ther. 2017;25:2062–74.
6. Du WW, Yang W, Chen Y, Wu ZX, Foster FS, Yang Z, Li X, Yang BB. Foxo3 circular RNA promotes cardiac senescence by modulating multiple
factors associated with stress and senescence responses. Eur Heart J. 2017;38:1402–12.
7. Zheng X, Chen L, Zhou Y, Wang Q, Zheng Z, Xu B, Wu C, Zhou Q, Hu W, Wu C, Jiang J. A novel protein encoded by a circular RNA circPPP1R12A promotes tumorogenesis and metastasis of colon cancer via Hippo-YAP signaling. Mol Cancer. 2019;18:47.
8. Koh W, Pan W, Gawad C, Fan HC, Kirccher GA, Wyss-Coray T, Blumenfeld EL, Sayed YY, Quake SR. Noninvasive in vivo monitoring of tissue-specific global gene expression in humans. Proc Natl Acad Sci USA. 2014;111:7361–6.
9. Li Z, Zheng X, Wu F, Wu L, Cao H, Wang Q, Tang W. The emerging landscape of circular RNAs in immunity: breakthroughs and challenges. Biomark Res. 2020;8:25.
10. Yang H, Zhang H, Yang Y, Wang X, Deng T, Liu R, Ning T, Bai M, Li H, Hong W, Xue M, Jiang J, Zhang Y, Gao X. Circular RNA circ-CPA4/let-7 miRNA-PD-L1 axis regulates cell growth, stemness, drug resistance and immune evasion in non-small cell lung cancer (NSCLC). J Exp Clin Cancer Res. 2020;39:149.
11. Hong W, Xue M, Jiang J, Zhang Y, Gao X. Circular RNA circ-CPA4/let-7 miRNA-PD-L1 axis regulates cell growth, stemness, drug resistance and immune evasion in non-small cell lung cancer (NSCLC). J Exp Clin Cancer Res. 2020;39:149.
12. Chen B, Huang S. Circular RNA: an emerging non-coding RNA as a regulator and biomarker in cancer. Cancer Lett. 2018;418:41–50.
13. Chen Y, Li C, Tu C, Liu X. Circular RNAs: a new frontier in the study of human diseases. J Med Genet. 2016;63:359–65.
14. Shang J, Chen WM, Liu S, Wang ZH, Wei TN, Chen ZZ, Wu WB. CircPAN3 contributes to drug resistance in acute myeloid leukemia through regulation of autophagy. Leuk Res. 2019;85:106198.
15. Che H, Ding H, Jia X. circ_0080145 Enhances imatinib resistance of chronic myeloid leukemia by regulating miR-326-PPFA1. Cancer Biother Radiopharm 2020.
16. Liu Z, Wang Q, Wang X, Xu Z, Wei X, Li J. Circular RNA circ-IARS regulates ferroptosis in HCC cells through interacting with RNA binding protein ALKBH5. Cell Death Discov. 2020;6:72.
17. Chen YG, Chen R, Ahmad S, Verma R, Kasturi SP, Amaya L, Broughton JP, YJ, El-Sayed YY, Quake SR. Noninvasive in vivo monitoring of tissue-specific global gene expression in humans. Proc Natl Acad Sci USA. 2018;115:9326–31.
18. Liu X, Abraham JM, Cheng Y, Wang Z, Wang Z, Zhang G, Ashktorab H, Ferran T, Ronan. Cancer Manag Res. 2019;11:30215–21.
19. Chen F, Wang X, Fu S, Wang S, Fu Y, Zhang J, Liu J, Liu Z. Circular RNA circ-CDY2 sponges miR-1180 to elevate yes-associated protein in multiple myeloma. Exp Biol Med (Maywood). 2020;245:925–32.
20. Zhou X, Chen N, Xu H, Zhou X, Wang J, Fang J, Zhang Y, Li, Yang J, Yang W. Regulation of Hippo-YAP signaling by insulin-like growth factor-1 receptor in the tumorigenesis of diffuse large B-cell lymphoma. J Hematol Oncol. 2020;13:77.
21. Feng Y, Zhang L, Wu J, Khadka B, Fang Z, Gu J, Tang B, Xiao R, Pan G, Liu J. CircRNA circ_0000190 inhibits the progression of multiple myeloma through modulating miR-767/-5p/MAPK4 pathway. J Exp Clin Cancer Res. 2019;38:54.
22. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
23. Wang Y, Lin Q, Song C, Ma R, Li X. CircRNA circ_0007841 promotes the progression of multiple myeloma through targeting miR-338-5p/BRD4 signaling cascade. Cancer Cell Int. 2020;20:383.
24. Xia X, Li X, Li F, Wu X, Zhang M, Zhou H, Huang N, Yang X, Xiao F, Liu D, et al. A novel tumor suppressor protein encoded by circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent Kinase-1. Mol Cancer. 2019;18:131.
25. Huang X, Li Z, Zhang Q, Wang W, Li B, Wang L, Xu Z, Zeng A, Zhang X, Zhang X, et al. Circular RNA AKT3 upregulates PIK3R1 to enhance cisp-10 resistance in gastric cancer via miR-198 suppression. Mol Cancer. 2019;18:71.
26. Li M, Meng F, Lu Q. Expression profile screening and bioinformatics analysis of circRNA, LncRNA, and mRNA in acute myeloid leukemia drug-resistant cells. Turk J Haematol. 2020;37:104–10.
27. Shang J, Chen WM, Wang ZH, Wei TN, Chen ZZ, Wu WB. CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p-XIAP axis. Exp Hematol. 2019;70:42–54.
28. Pan Y, Lou J, Wang H, An N, Chen H, Zhang Q, Du X. CircBA9.3 supports drug resistance in acute myeloid leukemia cells by regulating miR-1299 and miR-5007. Theranostics. 2020;10:30642–54.
29. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
30. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
31. Shang J, Chen WM, Wang ZH, Wei TN, Chen ZZ, Wu WB. CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p/XIAP axis. Exp Hematol. 2019;70:42–54.
32. Pan Y, Lou J, Wang H, An N, Chen H, Zhang Q, Du X. CircBA9.3 supports drug resistance in acute myeloid leukemia cells by regulating miR-1299 and miR-5007. Theranostics. 2020;10:30642–54.
33. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
34. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
35. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
36. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
37. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
38. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
39. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
40. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
41. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
42. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
43. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
44. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
45. Liu F, Wang YL, Wei JM. Huang ZD. Upregulation of circ_0000142 promotes multiple myeloma progression by adsorbing miR-610 and upregulating AKT3 expression. J Biochem. 2020.
49. Song Y, Hu N, Song X, Yang J. Hsa_Circ_0007841 Enhances multiple myeloma chemotherapy resistance through upregulating ABCG2. Technol Cancer Res Treat. 2020;19:153303820928371.

50. Zhu YF, Zheng Z, Xiang Y, Zhang Y. Glucose starvation-induced rapid death of Nrf1 alpha-deficient, but not Nrf2-deficient, hepatoma cells results from its fatal defects in the redox metabolism reprogramming. Oxid Med Cell Longev. 2020;2020:4959821.

51. Warburg O. On the origin of cancer cells. Science. 1956;123:309–14.

52. Lapa B, Goncalves AC, Jorge J, Alves R, Pires AS, Abrantes AM, Coucelo M, Abrunhosa A, Botelho MF, Nascimento-Costa JM, Sarmento-Ribeiro AB. Acute myeloid leukemia sensitivity to metabolic inhibitors: glycolysis showed to be a better therapeutic target. Med Oncol. 2020;37:72.

53. Xu Y, Zhou Y, Cao W, Liu H. Improved production of malic in aspergillus niger by abolishing citric acid accumulation and enhancing glycolytic flux. ACS Synth Biol. 2020;9:1418–25.

54. Chen X, Xu J, Tian H, Shan Z, Liu W, Pan Z, Ren J. Circular RNA hsa_circRNA_100290 serves as a ceRNA for miR-378a to regulate oral squamous cell carcinoma cells growth via Glucose transporter-1 (GLUT1) and glycolysis. J Cell Physiol. 2019;234:19130–40.

55. Zhang X, Wang S, Lin G, Wang D. Down-regulation of circ-PTN suppresses cell proliferation, invasion and glycolysis in glioma by regulating miR-432-5p/RAB10 axis. Neurosci Lett. 2020;731:153–51.

56. Zhu X, Du J, Gu Z. Circ-PVT1/miR-106a-5p/HK2 axis regulates cell growth, metastasis and glycolytic metabolism of oral squamous cell carcinoma. Mol Cell Biochem. 2020;474:147–58.

57. Yu T, Wang Y, Fan Y, Fang N, Wang T, Xu T, Shu Y. Circular RNAs in cancer metabolism: a review. J Hematol Oncol. 2019;12:90.

58. Andersen CJ, Dupree L, Murray K, Ragonesi N, McMullen K, Cintron-Oxid Med Cell Longev. 2020;2020:4959821.

59. Arcinas C, Tan W, Fang W, Desai TP, Teh DCS, Degirmenci U, Xu D, Foo R, et al. Induction of autophagy by valproic acid enhanced chronic myelogenous leukemia cell viability. Lipids 2020.

60. Ji MM, Wang L, Zhan Q, Xue W, Zhao Y, Zhao X, Xu PP, Shen Y, Liu H, et al. Induction of autophagy by valproic acid enhanced chronic myelogenous leukemia cell viability. Lipids 2020.

61. Yao H, Han B, Zhang Y, Shen L, Huang R. Non-coding RNAs and glucose-induced fibrosis in renal tubular cells via pyroptosis. Biol Pharm Bull. 2020;43:558–64.

62. Feng XQ, Nie SM, Huang JX, Li TL, Zhou JJ, Wang W, Zhuang LK, Meng FJ. Circular RNA circHIPK3 serves as a prognostic marker to promote chronic myeloid leukemia progression. Neoplasma. 2020;67:171–7.

63. Li JX, Zhang ZF, Wang XB, Yang EQ, Dong L, Meng J. PLZF regulates apoptosis of leukemia cells by regulating AKT/Foxo3a pathway. Eur Rev Med Pharmacol Sci. 2019;23:6411–8.

64. Yu T, Wang Y, Wu B, He D, Zhang C, Duan C, Li B. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol. 2019;12:34.

65. Zhou C, Molinie B, Daneshvar K, Porldick Jv, Wang J, Vann Beutenbergh N, Xing Y, Giallourakis C, Mullen AC. Genome-wide maps of m6A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs. Cell Rep. 2020;17:668–42.

66. Chen SJ, Zhou GB. Targeted therapy: the new lease on life for acute myeloid leukemia. Cell Stem Cell. 2019;25:137–48.

67. Wang M, Yang Y, Yang J, Yang J, Han S. circ_KIAA1429 accelerates hepatocellular carcinoma advancement through the mechanism of m6A-A-YTHDF3-Zeb1. Life Sci. 2020;257:118082.

68. Zhao L, Liu Y, Zhang J, Liu Y, Qi Q. LncRNA SNHG14/miR-5590-3p/ZEB1 positive feedback loop promoted diffuse large B cell lymphoma progression and immune evasion through regulating PD-1/PD-L1 checkpoint. Cell Death Dis. 2019;10:731.

69. Chen SJ, Zhou GB. Targeted therapy: the new lease on life for acute promyelocytic leukemia. J Hematol Oncol 2012;5:64-71.

70. Wang WT, Han C, Sun YM, Chen TQ, Chen YQ. Noncoding RNAs in cancer therapy resistance and targeted drug development. J Hematol Oncol. 2019;12:55.
93. Guarnerio J, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, Lo-Coco F, Tay Y, Beck AH, Pandolfi PP. Oncogenic role of fusion-circRNAs derived from cancer-associated chromosomal translocations. Cell. 2016;165:289–302.

94. Zhao X, Chen A, Yan X, Zhang Y, He F, Hayashi Y, Dong Y, Rao Y, Li B, Conway RM, et al. Downregulation of RUNX1/LBF2-beta by MLL fusion proteins enhances hematopoietic stem cell self-renewal. Blood. 2014;123:1729–38.

95. Dal Molin A, Bresolin S, Gaffo E, Tretti C, Boldrin E, Meyer LH, Guglielmelli P, Vannucci AM, Te Kronnie G, Bortoluzzi S. CircRNAs are here to stay: a perspective on the MLL reoccurrence. Front Genet. 2019;10:108.

96. Huang W, Fang K, Chen TQ, Zeng ZC, Sun YM, Han C, Sun LY, Chen ZH, Yang QQ, Pan Q, et al. circRNA circAF4 functions as an oncogene to regulate MLL-AF4 fusion protein expression and inhibit MLL leukemia progression. J Hematol Oncol. 2019;12:103.

97. Papaioannou D, Volinia S, Nicolet D, Swierenga M, Petri A, Mozek K, Bill M, Pepe F, Walker CJ, Walker AE, et al. Clinical and functional significance of circular RNAs in cytogenetically normal AML. Blood Adv. 2020;4:239–51.

98. Nagoshi H, Taki T, Hanamura I, Nitta M, Otsuki T, Nishida K, Okuda K, Tsutsumi Y, Chinen Y, Sakamoto N, Nagoshi H, Nishida K, Kobayashi S, Alberto L, Tolomeo D, Cifola I, Severgnini M, Turchiano A, Augello B, Guo S, Li B, Chen Y, Zou D, Yang S, Zhang Y, Wu N, Sheng L, Huang H, Yi YY, Yi J, Zhu X, Zhang J, Zhou J, Tang X, Lin J, Wang P, Deng ZQ. Derived from cancer-associated chromosomal translocations. Cell. 2014;123:1729–38.

99. Coco F, Tay Y, Beck AH, Pandolfi PP. Oncogenic role of fusion-circRNAs expressed in mammalian brain are highly abundant, conserved, and dynamically expressed. Mol Cell. 2015;58:870–85.

100. Li S, Ma Y, Tan Y, Ma X, Zhao M, Chen B, Zhang R, Chen Z, Wang K. Profiling and functional analysis of circular RNAs in acute promyelocytic leukemia and their dynamic regulation during all-trans retinoic acid treatment. Cell Death Dis. 2018;9:651.

101. Li W, Zhong C, Jia J, Li P, Cui B, Ji C, Li M. Characterization of hsa_circ_0004277 as a new biomarker for acute myeloid leukemia via circular RNA profile and bioinformatics analysis. Int J Mol Sci. 2017;18.

102. Fanale D, Taverna S, Russo A, Bazan V. Circular RNA in exosomes: Adv Exp Med Biol. 2018;1083:1709–17.

103. Wang G, Liu W, Zou Y, Wang G, Deng Y, Luo J, Zhang Y, Li H, Zhang Q, Yang Y, Chen G. Three isoforms of exosomal circPTGR1 promote hepatocellular carcinoma metastasis via the miR449a-MET pathway. EBioMedicine. 2019;40:432–45.

104. Wu Z, Sun H, Wang C, Liu W, Liu M, Zhu Y, Xu W, Jin H, Li J. Mitochondrial genome-derived circRNA mc-CCOX2 functions as an oncogene in chronic lymphocytic leukemia. Mol Ther Nucleic Acids. 2020;20:801–11.

105. Luo Y, Gui R. Circulating Exosomal circMYC is Associated with the recurrence and Bortezomib resistance in patients with multiple myeloma. Turk J Haematol. 2020.

106. Ho TT, Zhou N, Huang J, Koirala P, Xu M, Fung R, Wu F, Mo YY. Targeting non-coding RNAs with the CINPVR/293 system in human cell lines. Nucleic Acids Res. 2015;43:64.

107. Jest I, Shalamova LA, Gershegesen GK, Niepmann M, Bindereif A, Rossbach O. Functional sequestration of microRNA-122 from Hepatitis C Virus by circular RNA sponges. RNA Biol. 2018;15:1032–9.

108. Wu P, Mo Y, Peng M, Tang T, Zhong Y, Deng X, Xiong F, Guo C, Wu X, Li Y, et al. Emerging role of tumor-related functional peptides encoded by circular RNA. Genes (Basel) 2020, 11.

109. Yi Z, Li Y, Wu Y, Zeng B, Li H, Ren G, Wang X. Circular RNA 0001073 attenuates malignant biological behaviours in breast cancer cell and is delivered by nanoparticles to inhibit mice tumour growth. Onc Target. 2020;11:6157–69.

110. Wang W, Han Y, Jo HA, Lee J, Song YS. Non-coding RNAs shuttled via exosomes reshape the hypoxic tumor microenvironment. J Hematol Oncol. 2020;13:67.

111. Chen W, Quan Y, Fan S, Wang H, Liang J, Huang L, Chen L, Li Q, He P, Ye Y. Exosome-transmitted circular RNA hsa_circ_0051443 suppresses hepatocellular carcinoma progression. Cancer Lett. 2020;475:119–28.

112. Song H, Liu Q, Liao Q. Circular RNA and tumor microenvironment. Cancer Cell Int. 2020;20:211.

113. Zhang W, Zhao X, Wang Y, Ren F, Sun D, Yan Y, Kong X, Bu J, Liu M, Xu M, S. exoRBase: a database of circRNA, lncRNA and mRNA in human blood. Nucleic Acids Res. 2018;46:D925–9.

114. Chen W, Quan Y, Fan S, Wang H, Liang J, Huang L, Chen L, Li Q, He P, Ye Y. Exosome-transmitted circular RNA hsa_circ_0051443 suppresses hepatocellular carcinoma progression. Cancer Lett. 2020;475:119–28.

115. Song H, Liu Q, Liao Q. Circular RNA and tumor microenvironment. Cancer Cell Int. 2020;20:211.

116. Wang W, Han Y, Jo HA, Lee J, Song YS. Non-coding RNAs shuttled via exosomes reshape the hypoxic tumor microenvironment. J Hematol Oncol. 2020;13:6157–69.
134. Ji P, Wu W, Chen S, Zheng Y, Zhou L, Zhang J, Cheng H, Yan J, Zhang S, Yang P, Zhao F. Expanded expression landscape and prioritization of circular RNAs in mammals. Cell Rep. 2019;26:3444–60.
135. Liu M, Wang Q, Shen J, Yang BB, Ding X. Circbank: a comprehensive database for circRNA with standard nomenclature. RNA Biol. 2019;16:899–905.
136. Li L, Wu P, Wang Z, Meng X, Zha C, Li Z, Qi T, Zhang Y, Han B, Li S, et al. NoncoRNA: a database of experimentally supported non-coding RNAs and drug targets in cancer. J Hematol Oncol. 2020;13:15.

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