Role of circular RNA in hematological malignancies (Review)

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Abstract. Compared with linear RNA, circular RNAs (circRNAs) form a covalently closed circular continuous loop and are highly conserved, stable and tissue-specific. In recent years, circRNAs received considerable attention in the diagnosis, classification, treatment and prognosis of hematological tumors. circRNAs function as microRNA sponges and competitive endogenous RNAs that play an essential role in the translation, regulation and interaction of proteins. The present review discussed the fundamental properties and functions of circRNAs and the latest advancements in the context of circRNAs in the clinical research of hematological malignancies, namely acute and chronic myeloid leukemia, and chronic lymphocytic leukemia. circRNAs show potential in the diagnosis and prognosis of various diseases and can be used as therapeutic targets and biomarkers for disease.

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1. Introduction

Non-coding RNAs (ncRNAs), which account for 98% of human RNAs (1), do not encode proteins but play an important role in the regulation of gene expression, including transcription, translation and RNA splicing (2,3). NcRNAs include microRNAs (miRNAs/miRs), small nuclear RNAs, PIWI-interacting RNAs, long non-coding RNAs (lncRNA) and circular RNAs (circRNAs) (4,5). circRNAs are formed by back-splicing events where the 5' and 3' ends join to form covalently closed continuous loops without polyadenylated tails (6).There are three types of circRNAs: i) Exonic circRNAs (ecircRNAs; with one or more exons) (7,8); ii) exon-intron circRNA (EIcirRNA) (9); and iii) circularized intron RNA (ciRNA) (10). However, 85% of circRNAs originate from exons (2) (Fig. 1). circRNAs were initially considered as byproducts of transcription (11) after being first discovered in plant viruses in 1976 (12). However, the growing number of publications on circRNAs has illustrated the biological importance of circRNAs.

circRNAs can function as miRNA sponges. Certain circRNAs can act as competing endogenous RNAs that negatively influence miRNAs, thus regulating transcription and translation. Cerebellar degeneration-related protein 1 antisense RNA was reported to bind to miR-7, indicating that circRNAs have miRNA-binding capacity (3). miRNAs have antagonizing activities in the human and mouse brain (3), and can inhibit miR-7, thus increasing the expression levels of miR-7 targets, including epidermal growth factor receptor and insulin receptor substrate 2 (13). Besides, the testis-specific circRNA, sex-determining region Y was also reported to serve as a miR-138 sponge (13). The circRNA-miRNA-mRNA axis has critical functions in tumorigenesis (14). The function of certain circRNAs depends largely on their target pathways. For example, circ-itchy E3 ubiquitin protein ligase (ITCH) could increase the level of ITCH, which inhibits the Wnt/β-catenin pathway (15,16). circRNAs can act as platforms for protein interaction. For example, mannose binding lectin (Mbl) specifically binds to the circ-Mbl, which is generated from its own RNA (17), and circ-forkhead box O3 can inhibit cell-cycle progression by interacting with Cdk (18). circRNAs were reported to regulate translation and are naturally resistant to exonucleases (19). The presence of internal ribosome entry sites (IRESs) and appropriate open reading frames (ORFs) induce cap-independent translation (2). The ORF can be translated in an *Escherichia coli* cell-free translation

system (20). A recent study demonstrated that efficient circRNA translation occurred in HeLa cells, and circRNA can be translated without such particular sequences (21). Furthermore, ribosomes can be recruited to an internal initiation codon by IRES (21). Circ-ZNF609 was reported to be translated by this mechanism and its high degree of methylation facilitates its translational activity (22).

circRNAs are conserved, stable and specific to the developmental stages and tissues (23,24). In comparison with linear RNAs, circRNAs were reported to be highly conserved at the nucleotide level in several eukaryotes from yeast to human (23). Due to their natural resistance to exonucleases, circRNAs appear to be extremely stable transcripts with half-lives of >24-48 h (25). Multiple previous results of RNA sequencing (RNA-seq) from brain tissues and differentiated cell lines indicated that circRNAs are tissue-specific (24). The various expressions at different developmental stages of mouse brain suggest that characteristics of circRNAs may depend on the developmental stage (24,26).

The development of high-throughput RNA-seq technology (27) accelerated the discovery of various circRNAs. RNA libraries were established using Ribo-Zero (ribosome RNA depletion) and RNase R (28). Later, computational algorithms emerged for detecting circRNAs, which were most commonly found at back-splicing junctions (29).

CircBase (http://www.circbase.org/) (30) contains data from *Homo sapiens*, *Mus musculus*, *Caenorhabditis elegans*, *Drosophila melanogaster* and *Latimeria chalumnae* species. Specifically, the CircBase database contains sequences, gene descriptions and genomic locations. CIRCpedia v2 (http://www.picb.ac.cn/rnomics/circpedia) (31) provides circRNA annotation for six species (human, mouse, rat, zebrafish, fly and worm) and contains an analysis tool for investigating the differential expression of circRNAs. CircInteractome (http://circinteractome.nia.nih.gov) (32) contains 109 datasets of RNA-binding proteins and functions by searching RNA-binding sites. CircNet database (http://circnet.mbc.nctu.edu.tw/) (33) assembled by transcriptome sequencing datasets, containing circRNA, miRNA and gene networks, and tissue-specific circRNA expression profiles. CirclncRNAnet (http://app.cgu.edu.tw/circlnc) (34) provides networks of lncRNAs or circRNAs of interest, based on next-generation sequencing (NGS) data. CircRNADb (http://reprod.njmu.edu.cn/circrnadb) (35) focuses on protein-coding annotations and provides information on exon splicing, genome sequence, IRES, ORF and references. CircR2Disease (http://bioinfo.snnu.edu.cn/CircR2Disease/) (36) provides experimental evidence for the associations between circRNAs and diseases and helps find the appropriate algorithms or models for circRNA-disease associations. Tissue-specific circRNA database (http://gb.whu.edu.cn/TSCD) (37) provides tissue-specific circRNAs in the main tissues of humans and mice and provides evidence to identify new markers for organogenesis and development of diseases. Similarly, cancer-specific circRNA database (http://gb.whu.edu.cn/CSCD) (38) aims to identify cancer-specific circRNAs.

Exosomes are 50-140-nm nanovesicles that transport abundant bioactive substances (39), which enhance cell-to-cell communication (40). Li *et al* (41) reported that circRNAs are stable in exosomes and demonstrated that circ-isoleucyl-tRNA synthetase 1 in tumor cell-derived exosomes function in the metastasis of pancreatic cancer (42). Zhang *et al* (43) demonstrated that exosome circRNAs circ-DB promoted the tumor growth of hepatocellular carcinoma, through the absorption of miR-34a and activation of the USP7/Cyclin A2 pathway. Since circRNAs are abundant in exosomes, they may cause disease-specific differential gene expression (44) and serve as biomarkers.

The presence of circRNAs in human peripheral blood, including in serum (45), plasma (42) and peripheral blood mononuclear cells (46), and saliva (47) and bone marrow (48) indicates their potential as disease biomarkers. Furthermore, circRNAs play a critical role in the pathogenesis and diagnosis of cancers, including gastric cancer (49), breast cancer (50) and esophageal cancer (51). However, the roles and mechanisms of circRNAs in hematological malignancies have not been fully clarified. Hematological malignancies are diseases of unusual stem and progenitor cells, which originate from genetic and epigenetic changes resulting in the dysregulation of self-renewal, proliferation and differentiation of cells (52). The present review provided an overview of the recent advancements of circRNAs associated with hematological malignancies, including acute myeloid leukemia (AML), chronic myeloid neoplasms, B- and T-/natural killer (NK)-cell lymphoma and multiple myeloma (MM), and discussed their relevance to clinical practice.

2. Acute myeloid leukemia

AML is a class of highly heterogeneous diseases derived from bone marrow hematopoietic cells and is characterized by the rapid growth of abnormal white blood cells, reduction in the normal production of blood cells, and infiltration and disruption of other organs in the body (53-55). Over the past few years, NGS has revealed an accumulation of mutations in genes regulating the splicing process in ~10% of patients with AML (56), highlighting the important role of the alterations in gene regulation in the molecular pathogenesis of AML.

circ-Vimentin (VIM). VIM, a component of type III intermediate filament protein, is involved in the regulation of lymphocyte adhesion and transcellular migration, and is associated with poor clinical outcome in older patients with AML (57).

Yi *et al* (58) observed that circ-VIM expression level in *de novo* patients with AML (particularly patients with non-acute promyelocytic leukemia and cytogenetically normal patients with AML) was significantly upregulated compared with that in healthy controls. A receiver operating characteristic (ROC) curve analysis indicated that high expression level of circ-VIM may serve as a promising diagnostic biomarker and treatment target (58).

circ-PVT1 oncogene (PVT1). In AML, 8q24 amplifications were reported to be associated with two fusion genes, PVT1-zinc finger, MIZ-type containing 7 (NSMCE2) and BF104016-NSMCE2 (59,60). circ-PVT1, generated from exon 2 of PVT1, is highly expressed in gastric cancer (49), non-small cell lung carcinoma (61) and osteosarcoma (62) compared with levels in matched para-carcinoma tissue; circ-PVT1 is highly
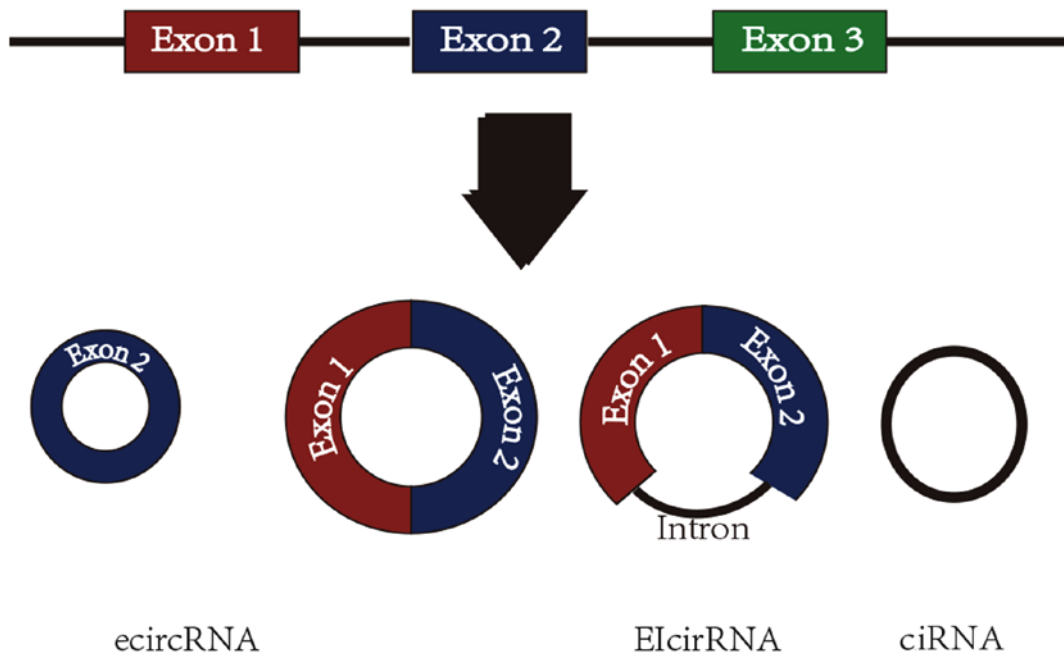
Figure 1. Biogenesis of ecircRNAs, EIciRNAs and ciRNA. The three main types of circRNAs are presented, such as ecircRNAs (one or more exons), EIcirRNA and ciRNA. circRNA, circular RNA; ecircRNAs, exonic circRNAs; EIcirRNA, exon-intron circRNA; ciRNA, circularized intron RNA.

expressed in head and neck squamous cell carcinoma and its expression is significantly associated with mutant p53 (63).

circ-PVT1 is highly expressed in AML compared with its level in normal bone marrow cells (48) and circ-PVT1 was found to act as a sponge for let-7 (64) and miR-125 families (65). Therefore, circ-PVT1 may be a potential novel therapeutic target.

hsa_circ_0004277. Li *et al* (66) reported that hsa_circ_0004277 expression was significantly lower in the AML group than in healthy controls and patients who entered complete remission (CR) post-treatment. These previous results indicated that hsa_circ_0,004277 variation is associated with AML progression.

Furthermore, hsa_circ_0004277 might be a diagnostic biomarker as well as a therapeutic target in AML (66). Additionally, hsa_circ_0004277 has several downstream targets including hsa-miR-138-5p, hsa-miR-30c-1-3p, hsa-miR-892b, hsa-miR-571 and hsa-miR-328-3p, revealed by bioinformatics analysis (66). Further downstream gene targets were predicted by bioinformatics analysis, with the most probable being SH3 domain containing GRB2 like 2, endophilin A1, PPARG coactivator 1α, phosphatidylinositol-5-phosphate 4-kinase type 2γ, SH2B adaptor protein 3, zinc finger protein 275 and ATPase Na⁺/K⁺ transporting family member β4 (66).

hsa_circ_0075001. Hirsch *et al* (67) reported a correlation between total nucleophosmin expression and hsa_circ_0075001. High hsa_circ_0075001 expression was strongly associated with a significantly lower expression of genes involved in the Toll-like receptor (TLR) signaling pathway (67). TLR1 expression was associated with leukemic stem cell survival in AML, as well as enhanced TLR1/TLR2 activation in leukemic stem cell differentiation (68,69). Thus,

hsa_circ_0075001 is a potential biomarker for classification and risk stratification.

circ-DLEU2. Wu *et al* (70) found that circ-DLEU2 was highly expressed in tissue samples from patients with AML and AML cell lines. Increased circ-DLEU2 resulted in promoted proliferation and inhibited apoptosis in AML cell lines. Furthermore, circ-DLEU2 suppressed miR-496 and further increased PRKACB expression (70).

circ-ANAPC7. Chen *et al* (71) compared the circRNA expression profile among five AML samples and five iron-deficiency anemia samples collected from donor bone marrow, which revealed 282 significantly upregulated and 416 downregulated circRNAs in patients with AML. Reverse transcription-quantitative PCR results indicated significant upregulation of circ-ANAPC7 in AML and suggested that circ-ANAPC7 was a potential biomarker for AML diagnosis and a potential novel therapeutic target. Further bioinformatics analysis indicated that circ-ANAPC7 may serve as a sponge for the miR-181 family (71).

circ-PAN3. Shang *et al* (72) compared the expression profiles of circRNAs between drug-resistant THP-1/ADM cell lines and naïve THP-1 cell lines. In total, 49 circRNAs showed significant differential expression. Meanwhile, overexpression of circ-PAN3 was identified in the bone marrow samples from patients with refractory/recurrent AML. circ-PAN3 had binding sites on miR-153-5p and miR-183-5p. Further experiments indicated that circ-PAN3 was possibly responsible for ADM resistance in AML and that circ-PAN3 regulated THP-1/ADM cells via the circ-PAN3-miR-153-5p/miR-183-5p-XIAP axis (72).

circ-HIPK2. Acute promyelocytic leukemia (APL) is a type of AML specialized for the promyelocytic leukemia-retinoic

Figure 2. Summary of circular RNAs in acute myeloid leukemia. The diagram illustrates the circRNA-miRNA-mRNA axis in AML studies. The overexpression of circular RNA (circ-VIM, circ-PVT1, circ-DLEU2, circ-ANAPC7 and circ-PAN3) in AML are marked in red and the downregulation of circular RNA (circ-HIPK2 and has-circ-0004277) are marked in green.

acid receptor α (PML/RARα) fusion protein, which induces oncogenic transcription by blocking cell differentiation at the promyelocytic stage, resulting in malignant transformation (73).

Ribo-minus RNA-seq analysis revealed 4,313 APL-expressed circRNAs in NB4 cell lines (74). Moreover, 508 circRNAs were dynamically expressed during all-trans retinoic acid treatment. circ-HIPK2 was downregulated in samples of patients with APL compared with that in healthy control samples and other subtypes of AML cases. The expression level of circ-HIPK2 was elevated significantly when patients with APL achieved CR (74). Ina previous study, circ-HIPK2 was found to function as a competing endogenous RNA, sponging miR-124, regulating astrocyte activation (75). Furthermore, miR-124a inhibited the downstream protein CEBPA (76). Therefore, circ-HIPK2 may affect APL differentiation through the miR-124-3p-CEBPA axis (74). The association of circRNAs expression in AML is shown in Fig. 2.

3. Chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a stem cell disorder of uncontrolled myeloid proliferation characterized by the Philadelphia chromosome (77). The reciprocal translocation t(9;22) (q34; q11.2), results in the BCR-ABL1 fusion. The progression of the disease involves 2-3 phases: Indolent chronic phase (CP), accelerated phase and blast phase (77,78). The introduction of imatinib and other tyrosine kinase inhibitors (TKIs) can change the disease course; however, resistance develops in ~13% of patients (78).

circ-BA9.3. Fusion genes, encoded by abnormal chromosomal translocations were associated with hematological

malignancies (79). Guarnerio *et al* (80) reported that tumors harbor circRNAs derived from chromosomal translocations and genomic fusion, which form aberrant fusion-circRNAs (f-circRNA). Furthermore, such f-circRNAs can be functionally relevant and tumor-promoting, with potential diagnostic and therapeutic implications (80). F-circRNAs such as PML-RARα and MLL-AF9 were found in hematological malignancies (80). The oncogene BCR-ABL1, which encodes a hyperactive tyrosine kinase, was found to be the most important factor that led to CML pathogenesis (81,82). TKIs induce long-lasting remission in patients with CML; however, 8-13% of chronic CML cases were resistant to imatinib, and ~18% of patients in the CP of CML lost their sensitivity to imatinib and suffered from relapse and progression (83).

Pan *et al* (84) reported that circ-BA9.3, a f-circRNA with 1,137 nucleotides, was the circular RNA of BCR-ABL1, and was found in 30 patients with CML, including 23 with imatinib-resistant and seven with imatinib-sensitive CML. circ-BA9.3 can improve the translation efficiency of BCR-ABL1 or prevent the oncoprotein from degrading (84). Additionally, the authors reported that circ-BA9.3 may cause severe carcinogenicity and resistance to TKI, such as imatinib, dasatinib and nilotinib by increasing the protein level of the BCR-ABL1 oncogene (84). circ-BA9.3 is involved in TKI resistance and may be a target for the diagnosis and treatment of patients with CML (84).

hsa_circ_0080145. Using high-throughput sequencing technology, Liu *et al* (85) identified 361 circRNAs that were aberrantly expressed in CML. Among these, hsa_circ_0080145 was significantly upregulated in CML.

ceRNA regulatory network analysis revealed that hsa_circ_0024002, hsa-circ_0080145 and hsa_circ_0037781

Table I. circRNAs and their utility in haematological malignancies.

Type of cancer	circRNA	Upregulated/downregulated in cancer	Function	(Refs.)
AML	circ-VIM	Upregulated	Diagnostic biomarker, treatment target	(58)
	circ-PVT1	Upregulated	Therapeutic target	(48)
	hsa_circ_0004277	Downregulated	Diagnostic biomarker, therapeutic target	(66)
	hsa_circ_0075001	Upregulated	Classification	(67)
	circ-DLEU2	Upregulated	Diagnostic biomarker	(70)
	circ-ANAPC7	Upregulated	Diagnosis or therapeutic target	(71)
	circ-PAN3	Upregulated	Potential target for drug resistance	(72)
	circ-HIPK2	Downregulated	Therapeutic target	(74)
CML	circ-BA9.3	Upregulated in resistant CML	Diagnostic biomarker, therapeutic target	(84)
	hsa_circ_0080145	Upregulated	Prognosis biomarker, therapeutic target	(85)
CLL	circ-CBFB	Upregulated	Therapeutic target	(91)

circRNA, circular RNA; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoblastic leukemia; VIM, vimentin; PVT1, plasmacytoma variant translocation 1; DLEU2, deleted in lymphocytic leukemia 2; ANAPC7, anaphase promoting complex subunit 7; PAN3, poly(A) specific ribonuclease subunit; HIPK2, homeodomain interacting protein kinase 2; CBFB, core-binding factor subunit β.

had the most target miRNAs, including leukemia-associated miRNAs, such as miR-16, miR-181a and miR-29b, among the differentially expressed circRNAs. miR-16 is upregulated in the peripheral lymphoid (86) and miR-181a inhibits vascular inflammation in human macrophages, suggesting that these circRNAs may be involved in the pathogenesis of CML (87). Furthermore, the miR-29 family is associated with malignant hematopoiesis and downregulated the expression of BCR-ABL1 (88).

Notably, hsa_circ_0080145 was upregulated in samples of patients with CML, as well as in CML cell lines. The dual luciferase reporter assay showed a sponge function of hsa_circ_0080145 for miR-29b. Therefore, circ_0080145 may be a potential prognostic and therapeutic biomarker for CML (85).

4. Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most frequently occurring leukemia in adults, characterized by significant expansion of dysfunctional B cells with co-expression of CD5, CD19, CD20 and CD23 in the peripheral blood, lymphoid organs and bone marrow (89). The diagnosis of CLL is mainly based on the precise immunophenotype of peripheral blood or bone marrow lymphocytes (90).

Xia et al (91) reported that circ-CBFB (hsa_circ_0000707), derived from the CBFB transcript (NM_001755), was significantly overexpressed in CLL compared to that in healthy controls. In addition, circ-CBFB regulates proliferation and inhibits apoptosis of CLL cells (91).

High circ-CBFB expression is an independent prognosis factor in patients with CLL. Mechanistically, circ-CBFB acts as a sponge for miR-607 and causes increased expression of the downstream target FZD3, thus regulating the activation of the Wnt/β-catenin pathway in CLL (91). The hyperactivation of FZD3 is known to be associated with CLL hematopoiesis (92). In summary, the circ-CBFB-miR-607-FZD3-Wnt/β-catenin axis is a potential target for CLL therapy. The expressions and functions of circRNAs in leukemia are shown in Table I.

5. B-cell lymphoma and multiple myeloma

Dahl et al (93) performed RNA-seq profiling of various lymphomas and multiple myeloma cell lines including four different mantle cell lymphoma (MCL) cell lines, REC-1, Granta-519, UPN2 and Z138, and the MM cell line, NCI-H929. Additionally, a novel circRNA derived from IKZF3 was detected, which is highly expressed in NCI-H929 (93). circRNAs from genes involved in lymphomagenesis and the development of MM were also detected, including FOXP1, SETD3, EZH2, ATM, XPO1, IKZF3, CD11A and WHSC1.

The differential expression levels of various circRNAs in different B-cell malignancies may potentially assist in distinguishing between different B-cell malignancies in the near future.

6. Conclusions

With the development of NGS and bioinformatics techniques, the importance of ncRNAs in tumor studies has been demonstrated in recent years (4). circRNAs have become topic of interest due to their biological functions, including the modulation of miRNA activity, protein interaction and regulation of translation (6,17,19). circRNAs have promising potential to serve as diagnostic, prognostic biomarkers and therapeutic

targets for diseases (48,58,66,70,71,74). The present review summarizes the function of differentially expressed circRNAs that contribute to the pathogenesis, diagnosis, treatment and prognosis of various hematological malignancies.

The detailed mechanisms and the function of the specific circRNAs mentioned in the present review remain to be clarified. In the future, circRNAs that have been thoroughly explored in preclinical studies should be further studied in clinical settings in order to be potentially used as biomarkers for timely diagnosis and as therapeutic targets for the treatment of various diseases.

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Authors' contributions

MM, YW, ZL and MZ contributed to the concept and collated the references, and MM draft the manuscript, ZL and MZ reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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