Exosomal circular RNAs in acute myeloid leukemia: Current updates and future prospects (Review)

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Abstract. Acute myeloid leukemia (AML) is form of cancer that affects the bone marrow and blood and is characterized by the rapid proliferation of abnormal white blood cells that transfer normal cells. Circular RNAs (circRNAs) constitute a set of special RNAs resulting from the involving from the downstream splice donor and upstream splice acceptor. Several studies have verified that circRNAs have various functions in cancer cells, either by promoting or inhibiting tumor progression and harmonizing the biological activities of malignant tumors, as well as cell proliferation, invasion, migration and metastasis. Exosomal circRNAs have emerged as potential biomarkers for a variety of diseases, such as cancer. They play a critical role in cancer metastasis. CircRNAs are stable and resistant to degradation compare to linear RNAs. They exhibit severak advantages as biomarkers, including abundance, stability and specificity. Exosomal circRNAs plays various roles in cancer cells due to their intercellular communications. The present review mainly focuses on the role of exosomal circRNAs in AML, and their role as biomarkers in diagnosis, prognosis and treatment response. Furthermore, the present review discusses various avenues of exosomal circRNAs for therapeutic intervention, which may lead to the deepened of novel effective management strategies for AML.

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1. Introduction

Acute myeloid leukemia (AML) is a form of cancer that affects the blood and bone marrow, characterized by the rapid proliferation of abnormal white blood cells (WBCs) that displace normal cells and may become life-threatening if left untreated (1). The accumulation of immature myeloid cells interferes with the production of WBCs, red blood cells (RBCs) and platelets, resulting in symptoms such as fever, fatigue, bruising and an increased risk of acquiring infections (2). AML occurs due to mutations in certain genes or chromosomes, such as Ras, FLT3, c-kit, translocation between chromosomes 8 and 21 and the inversion of chromosome 16. It mainly affects individuals aged ≥60 years (3). The term 'acute' refers to the rapid onset and progression of the disease, including the presence of immature myeloid cells, known as blasts, in blood and bone marrow (2). AML comprises of different subtypes, including acute promyelocytic leukemia (APL), acute monocytic leukemia (AML-M5), acute megakaryocytic leukemia (AML-M7) and other myeloid leukemia variants. These subtypes affect blood cell development at different stages, cause distinct symptoms and respond differently to treatment (4). Although AML includes several biologically distinct subtypes (e.g., APL and AML-M4/M5), in the current literature, there appears to be an absence of the subtype-specific profiling of exosomal circular RNAs (circRNAs) (5). The majority of studies have assessed either intracellular circRNAs or have evaluated single exosomal circRNAs in unstratified AML cohorts (6). To the best of our knowledge, comprehensive analyses comparing exosomal circRNA expression across AML subtypes have not yet been conducted, limiting conclusions on diagnostic or prognostic specificity (7). Even though outcomes for patients with AML are often described as 'poor', some patients can be cured and survival rates can be improved. The standard chemotherapeutic regimen for AML involves a combination of cytarabine and anthracycline that has been used for >40 years. Recent breakthroughs in molecular and cell biology have enhanced the

understanding of the pathophysiology of AML and the available treatment strategies, and has improved the identification of patients who are at a higher risk of developing leukemia (8). These advancements result in an increased number of treatment options for numerous patients and may provide future opportunities to reduce or prevent the progression of AML (9).

CircRNAs comprise a diverse and stable class of RNA molecules generated through the linkage of a downstream splice donor to an upstream splice acceptor. Certain circRNAs function as microRNA (miRNA/miR) sponges in the cytoplasm, while others in the nucleus enhance the expression of their parental genes through interactions with RNA polymerase II (10). Recently, novel peptides translated from circRNAs have been identified; for example, the SHPRH protein encoded by circSHPRH is expressed in normal brain tissue (11,12). Numerous studies have demonstrated that circRNAs are deregulated in cancer and leukemia (13,14), contributing to disease pathogenesis and cancer hallmarks (15).

Exosomes, initially reported to contain mRNA and miRNA, have since been shown to harbor various small non-coding RNA (ncRNA) species, in addition to long ncRNAs (lncRNAs), mRNAs and miRNAs (16,17). Notably, large amounts of circRNAs have been detected in exosomes, highlighting their high enrichment and stability primarily in tumor-derived exosomes compared to the circRNA levels in the parent cells.

In 2019, 61,559 new AML cases were reported among individuals aged 60-80 years, with 5,362 associated deaths and an estimated 990,656 disability-adjusted life years lost (18). The number of annual cancer cases in India doubled between 1990 and 2013. Of note, ~1.39 million cancer cases were reported in India in 2020, increasing to 1.42 million and 1.46 million in 2021 and 2022, respectively (19,20).

2. Exosomes

Extracellular vesicles (EVs) are small, membrane-bound structures enclosed by a lipid bilayer and released by all types of cells. These vesicles play crucial roles in cell-to-cell communications and transport a variety of biomolecules, including proteins, lipids and nucleic acids. EVs are typically categorized into different types based on their origin. Microvesicles range in size from 30 to 5,000 nanometers, while exosomes, a type of EV, contain cargoes such as DNA, RNA, lipids and proteins (21). Based on their biogenesis and size, EVs are generally classified into three groups, namely microvesicles, exosomes and apoptotic bodies (22): i) Microvesicles bud directly from the plasma membrane and range from 100 to 1,000 nm in size; ii) exosomes are produced by the fusion of multivesicular bodies with the plasma membrane and range from 30 to 150 nm in size; and iii) apoptotic bodies are released by dying cells into the extracellular space and range from 50 to 5,000 nm in diameter (21,23).

In multicellular organisms, exosomes are found in a variety of biological fluids, including cerebrospinal fluid, urine, blood and saliva. Their composition is influenced by the physiological state, environmental stimuli and characteristics of the parent cells. Exosomes contain diverse proteins, such as membrane, extracellular matrix and nuclear proteins, as well as nucleic acids including DNA, mRNA and various ncRNAs. Cytosolic metabolites are found in some cases (23). Notably, circRNAs are incorporated into exosomes more than their linear analogue (24). Various studies have demonstrated the roles of circRNAs in AML, demonstrating that they can either promote or inhibit tumor development and regulate key malignant behaviors, such as proliferation, metastasis, invasion and migration (25). In cancer, exosomes aid in the communications between tumor cells and the surrounding microenvironment (26). However, circRNAs within exosomes have not extensively investigated. Recent research indicates that exosome-associated circRNAs result in cancer progression, in the formation of premetastatic niches and metastatic spread (27). Exosomes may also participate in tumor immune regulation and support cancer therapy (28). The comparison of exosomal circRNAs comparison between patients with cancer and healthy individuals has revealed substantial differences, suggesting their clinical relevance and research potential (29). Exosomes further contribute to tumor biology by enabling horizontal transfer, thereby transporting various cargoes from donor cells to recipient cells located either locally or at distant sites (30). Communication between malignant cells and surrounding normal or tumor-associated cells via exosomes significantly influences tumor progression.

Biogenesis of exosomes. Exosome biogenesis begins with an endocytic event at the plasma membrane. The most well-described mechanism for exosome formation is driven by the endosomal sorting complex required for transport (ESCRT), along with a multimolecular machinery that operates at the endosomal membrane during the various stages of exosome biogenesis. Although ESCRT complexes (TSG101, ALIX and VPS proteins) regulate membrane budding and cargo selection, current evidence indicates they do not directly recognize circRNA sequences (31). The selective loading of circRNAs into exosomes is predominantly mediated by RNA-binding proteins (RBPs), such as hnRNPA2B1, YBX1, FUS and QKI, which bind specific sequence motifs or secondary structures, including the exosome-enrichment motif 5'-GMWGVWGRAG-3' reported in circRNAs (32). These RBPs recruit circRNAs to sites of intraluminal vesicle formation, while ESCRT machinery facilitates vesicle scission (33). Emerging evidence suggests that AML blasts exhibit an increased exosomal output and an enhanced enrichment of oncogenic circRNAs compared to normal hematopoietic cells, likely due to dysregulated RBP expression, altered MVB dynamics and leukemic stress pathways (34). However, AML-specific circRNA-sorting mechanisms remain incompletely defined and warrant further investigation. Exosomes are synthesized from multivesicular bodies (MVBs). The formation of MVBs can occur through ESCRT-independent pathways and is influenced by lipid components such as plasma-membrane-derived lipids and ceramides (35). Additionally, MVB formation is regulated by syndecan heparan sulfate proteoglycans and the cytoplasmic adaptor protein syntenin. Rab GTPases and soluble N-ethylmaleimide-sensitive factor attachment protein receptors facilitate either the fusion of MVBs with lysosomes for degradation or their docking at the cell periphery for exosome secretion (36). Moreover, research indicates that the elevated expression of p53, pyruvate kinase M2 and tumor suppressor-activated pathway 6 enhances exosome secretion

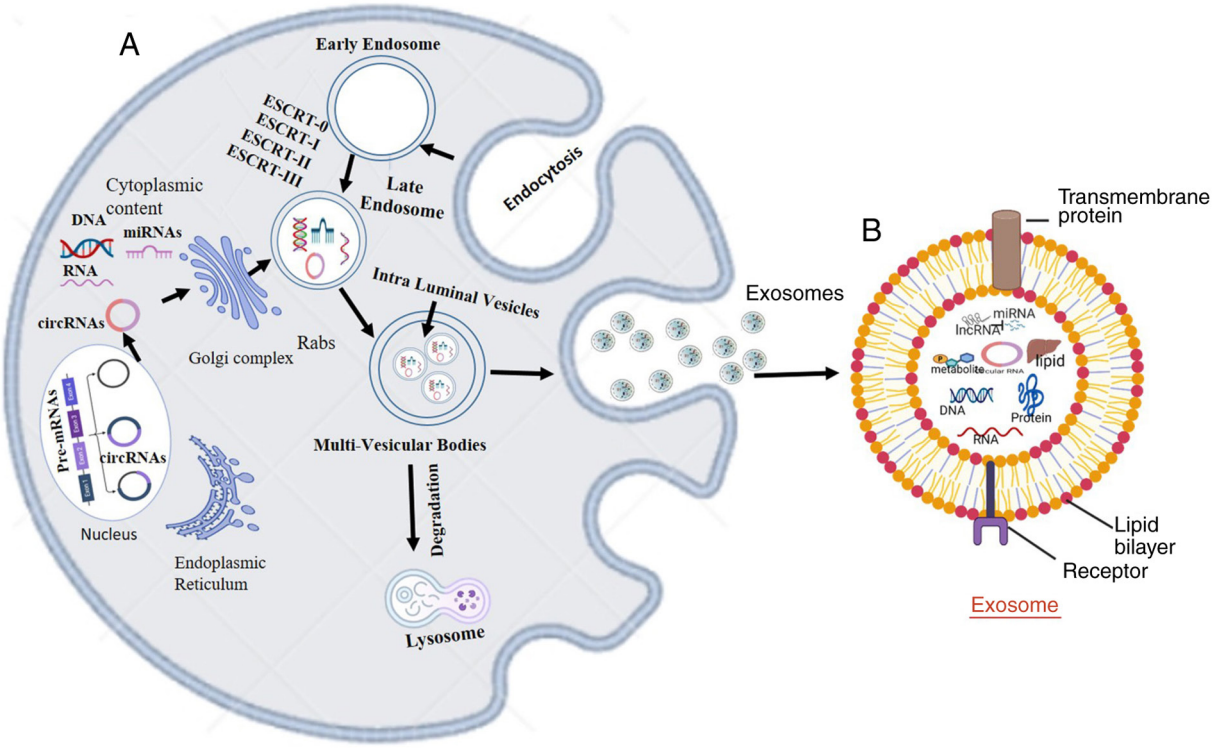

Figure 1. Biogenesis and secretion of exosomes. (A) The invagination of plasma membrane leads to the early formation of endosomes, which mature into late endosomes and are fused with the multivesicular bodies, resulting in the released of intra luminal vesicles as exosome sinto the extracellular space. (B) The released exosome containing circular RNA.

in tumor cells (37). Exosome release has also been shown to be influenced by changes in the microenvironment, including altered pH and the accumulation of intracellular Ca^{2+} ions (37). Exosomes are taken up by target cells through several mechanisms, such as endocytosis and direct membrane fusion (35). It has been demonstrated that exosome entry can be inhibited under certain conditions; for example, the internalization of exosomes by ovarian cancer cells via multiple endocytic pathways is significantly reduced at 4˚C (38). The mechanisms of exosome biogenesis are illustrated in Fig. 1.

Biogenesis of circRNAs. The biogenesis of circRNAs occurs through the back-splicing of pre-mRNA, in which a downstream splice donor site (5'splice site) attaches to an upstream splice acceptor site (3'splice site), and through transcription mediated by RNA polymerase II. Various circRNAs can be synthesized by the alternative back-splicing of the same sequence (39). However, the exact mechanisms that determine circRNA formation have not yet been fully delineated. CircRNAs are classified into three main categories based on their structure and mode of circularization: Circular intronic RNAs (ciRNAs), exonic circRNAs (ecircRNAs), and exon-intron circRNAs (EIciRNAs). EcircRNAs consist of one or more exons and are sometimes generated through alternative splicing that are primarily located in the cytoplasm (40). Several models have been proposed to explain the biosynthesis of ecircRNAs, including RBP-mediated circularization, lariat-driven circularization and intron-pairing-driven circularization. In the lariat-driven model, partial RNA folding occurs during pre-mRNA transcription, leading to exon skipping as the RNA folds. These structural changes can produce lariat intermediates containing initially non-adjacent exons along with their introns. CircRNAs are generated after intron sequences are removed through splicing within the lariat structure (41). In the intron-pairing-driven model, reverse complementary sequences within introns on both sides of the pre-mRNA facilitate complementary base pairing, mediating circularization. RBPs acting as trans-acting activators or inhibitors also play key roles in regulating circRNA production. DHX9, an abundant nuclear RNA helicase and ALU-element-binding protein, functions as an antagonist of circRNA biosynthesis. The lLoss of DHX9 increases circRNA production by allowing the formation of RNA pairs flanking circularized exons (40). Additionally, several splicing factors can bind specific RNA motifs and regulate circRNA biogenesis. Quaking (QKI), a mesenchymal splicing factor, is crtiical for generating circRNAs during epithelial-mesenchymal transition. The RBP FUS regulates back-splicing reactions and thus controls circRNA formation in mouse embryonic-stem-cell-derived motor neurons. While numerous RBPs, such as QKI, DHX9, hnRNPA2B1 and FUS regulate circRNA circularization, AML-specific alterations in these RBPs remain poorly defined (42). Available transcriptomic datasets indicate that DHX9 is not downregulated in AML, but is often upregulated; however, to date, at least to the best of our knowledge, no study has demonstrated a direct link between DHX9 expression and increased cellular or exosomal circRNA production in leukemic cells (43). Similarly, although QKI is a major enhancer of back-splicing, recurrent QKI mutations have not been reported in AML, and changes in QKI expression across AML subtypes have not been shown to modify circRNA biogenesis. Moreover, although specific AML driver

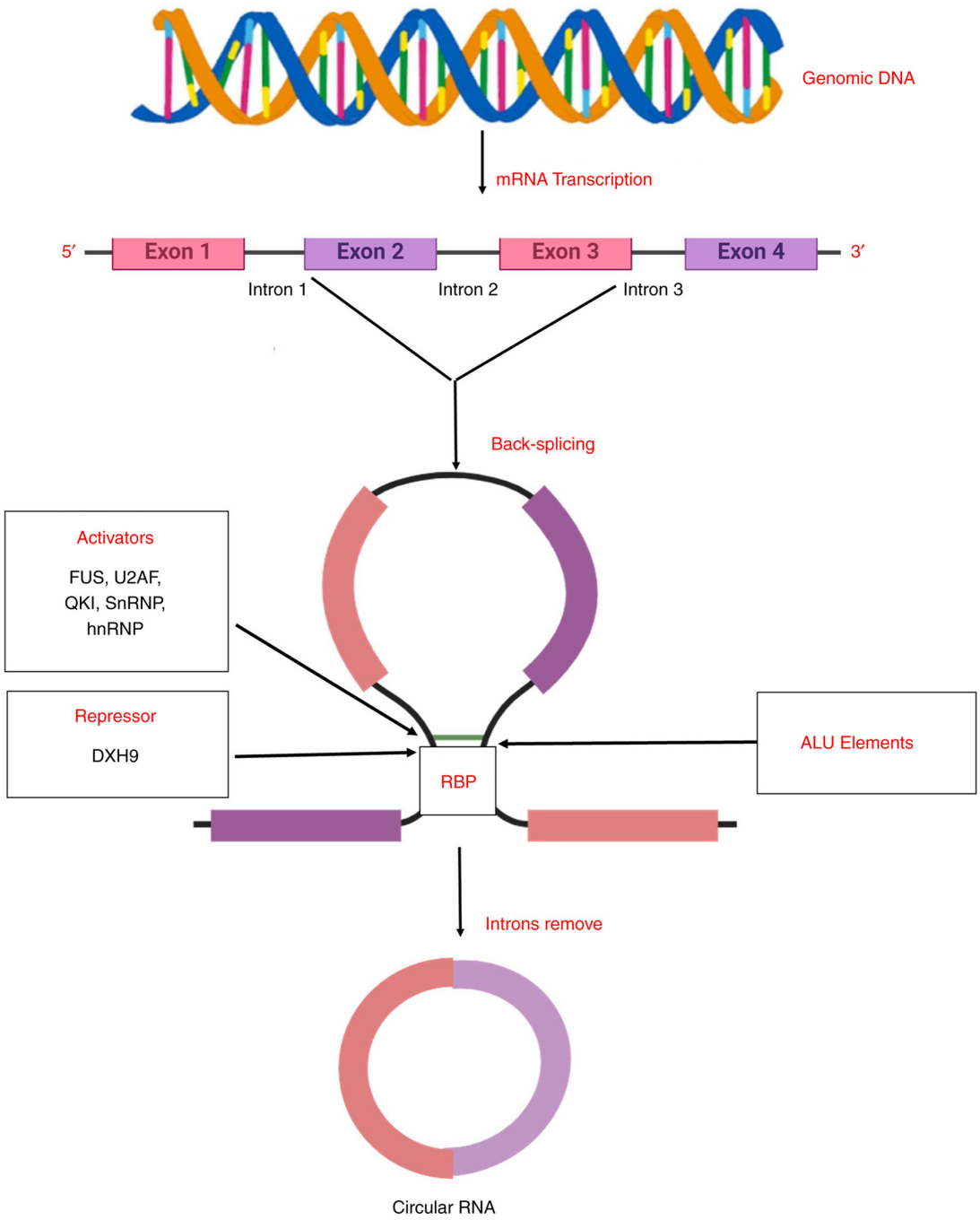

Figure 2. Biogenesis of exosomal circular RNA. Splicing; the pre-cursor mRNA undergoes splicing, in which the introns are removes (non-coding regions) and joins exons (coding regions) together. Circularization; in this step, the spliced RNA is circularized through a process called back splicing, where the splice donor site of one exon is joined to the splice acceptor site of another exon.

lesions [e.g., FLT3-ITD, NPM1 mutations, t(8;21)] have been associated with altered circRNA expression patterns, there is currently no evidence that these mutations directly disrupt intronic complementary sequences or intron-pairing mechanisms that determine circRNA formation (25,44). Thus, the influence of AML-associated RBPs and genomic lesions on circRNA circularization and exosomal loading remains an important but unresolved area for future investigation (34). EIciRNAs are primarily located in the nucleus and consist of exons and introns that are retained during splicing. These EIciRNAs play a crucial role in regulating the transcription of their parental genes (45). During the formation of ecircRNAs, the introns flanking the exons are typically spliced out; however, when these introns are retained, EIciRNAs are formed. Some lariat structures are produced during splicing from introns where most of them are rapidly degraded through debranching (40). A schematic illustration of the biogenesis of exosomal circRNAs is presented in Fig. 2.

3. Functions of exosomal circRNAs in AML

In recent years, circRNAs have gained attention due to their diverse functions and regulatory roles in various biological processes, including cancer. In AML, circRNAs are recognized

Table I. Different types of exosomal circRNAs in AML and their roles and pathways.

Exosomal circRNA	Roles	Pathways	(Refs.)
circRNA-0004913	Regulates AML progression and chemo resistance	Likely involves pathways related to cell proliferation, survival, and drug resistance	(117)
circRNA-300445163	Associated with AML diagnosis and prognosis	Pathways related to leukemogenesis, survival and disease.	(118)
circRNA-0012152	Regulates AML cell proliferation and invasion	Signaling pathways related to cell proliferation, Invasion, and apoptosis	(119,120)
circRNA-0025202	Involved in AML pathogenesis and progression	Pathways associated with leukemogenesis, cell survival, and proliferation	(121)
circRNA-0033386	Acts as a molecular sponge for miR-1200	Regulatory pathways modulated by miR-1200, impacting cell proliferation and survival	(117)
circRNA-0042853	Reduces AML cell proliferation and apoptosis	Pathways regulating cell cycle development, apoptosis, and leukemogenesis	(75)

AML, acute myeloid leukemia.

as potential biomarkers and regulators of disease development and progression (46). The dysregulated expression of circRNAs in patients with AML has been linked to cellular processes associated with the pathogenesis of AML, such as apoptosis, proliferation, cell differentiation and drug resistance. For example, circ_0009910 has been shown to function as a sponge for miR-20a-5p, thereby influencing the expression of RUNX1, which promotes the progression of AML by inhibiting apoptosis and increased cell proliferation, leading to disease development (25). By contrast, circ_0004277 has been found to be downregulated in AML. Circ_0004277 upregulates its target gene, SSBP2, by sequestering miR-134-5p and resulting in the inhibition of the PI3K/AKT signaling pathway and the suppression of AML cell invasion and proliferation (47). CircRNAs have also been implicated in regulating the response of AML cells to chemotherapy. For instance, circ_100053 upregulates TCL1A by sponging miR-29b-3p. The increased expression of circ_100053 enhances CML cell resistance to imatinib, a commonly used chemotherapeutic drug by promoting cell proliferation and inhibiting apoptosis (48). Similarly, resistance to vincristine has been shown to be associated with the overexpression of circPVT1 in patients with AML (49). Conversely, some circRNAs enhance sensitivity to anti-leukemic drugs, as observed with the knockdown of the fusion circRNA, circM9 (50). Overall, circRNAs play vital roles in the pathogenesis of AML by regulating various signaling pathways and cellular processes (51). Dysregulated circRNAs may provide novel therapeutic strategies for the treatment of AML. However, further studies are required to fully understand the functions and biogenesis of circRNAs in AML and to explore their potential clinical applications as biomarkers (52). Various types of circRNAs and their roles in AML are presented in Table I.

Exosomal circRNAs in the progression/development of AML. Several studies have demonstrated that circRNAs function in AML by either promoting or inhibiting tumor progression, and modulating the biological behavior of malignant cells, including proliferation, invasion, migration, and metastasis (53,54). Exosomal circRNAs perform all of the aforementioned roles in cancer due to their ability to mediate intercellular communication. When exosomal circRNAs are taken up by target cells, they influence the physiological and pathological states of those cells (55). Numerous studies have examined the mechanisms through which exosomal circRNAs contribute to cancer progression and development. Exosomal circRNAs are circular RNAs enclosed within exosomes where small extracellular vesicles released by cells into bodily fluids such as saliva, blood and urine. These exosomal circRNAs participate in cell-cell communications, other biological processes and disease progression (56). Circ-ITCH has been shown to promote the progression of hepatocellular carcinoma by sponging miR-214. By sequestering miR-20b-5p, circ-ITCH reduces its inhibitory effect on the target gene PTEN, leading to activation of the PTEN/PI3K/AKT signaling pathway, which enhances cell proliferation and inhibits apoptosis (57).

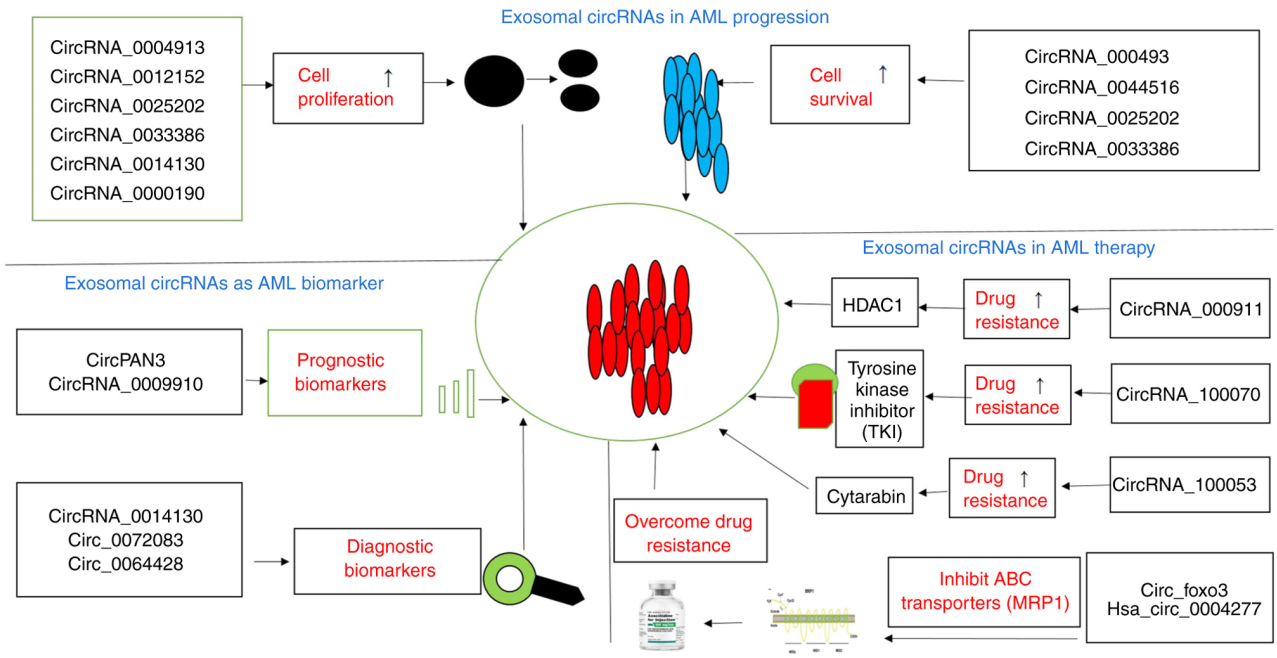

Figure 3. (Top panel) Different examples of exosomal circular RNAs which play a crucial role in AML progression. CircRNA_0004913, CircRNA_00012152, CircRNA_0025202, CircRNA_0033386, CircRNA_0014130 and CircRNA_0000190 are involved in cell proliferation, while CircRNA_000493, CircRNA_0044516, CircRNA_0025202 and CircRNA_0033386 are involved in cell survival. (Bottom left panel) Exosomal circular RNA as AML biomarkers. The following circRNAs, i.e., Circ_PAN3 and CircRNA_0009910 are prognostic biomarkers and CircRNA_0014130, Circ_0072083 and Circ_00064428 are diagnostic biomarkers. (Bottom right panel) Different exosomal circular RNAs involved in AML therapy. These includes CircRNA_000911, CircRNA_100070, and CircRNA_100053 which facilitates drug resistance while Circ_foxo3 and Has_circ_0004277 which overcome drug resistance by inhibiting ABC transporters. AML, acute myeloid leukemia.

Exosomal circRNAs further promote cell proliferation and survival by modulating the expression of genes involved in cell-cycle progression and apoptosis. CircRNA_0014130, for instance, has been identified as an oncogenic driver in AML by sponging miR-139-5p/miR-141-3p and activating the β-catenin signaling pathway, thereby contributing to the development of AML (25). Similarly, circRNA_100290 has been shown to be transferred from AML cells to bone marrow stromal cells, where it upregulates CXCL16 expression. CXCL16, in turn, supports the progression and invasion of AML cells within the bone marrow microenvironment, promoting disease development (58). Exosomal circ_0004136 was among the first circRNAs implicated in AML: The knockdown of circ_0004136 was shown to reduce AML cell viability, migration, invasion and promoted apoptosis, whereas its overexpression was shown to enhance proliferation and invasive behavior *in vitro* (59). Mechanistic studies link circ_0004136 to the miR-570-3p/TSPAN3 axis. As circ_0004136 was detected in AML serum exosomes, it is considered a promising non-invasive biomarker and a potential therapeutic target (60). While earlier studies focused on intracellular circ_0009910 (61), more recent research indicates that it is enriched in AML-derived exosomes: Exosomal circ_0009910 promotes the proliferation, reduces the apoptosis and regulates the cell cycle of AML cell lines (61). The functional mechanism involves the sponging of miR-5195-3p, leading to the upregulation of GRB10, which drives leukemic cell survival and proliferation. These data indicate that exosomal circ_0009910 may contribute to AML pathogenesis via intercellular signaling through EVs (51). Exosomal circRNAs affect the antitumor immune microenvironment and promote immune evasion and thus regulate immune response in AML (62). CircRNA_0000190 upregulates CD96 by sponging miR-142-3p, which suppresses proliferation and the cytotoxic activity of natural killer cells (61). Certain circRNAs activate pro-inflammatory signaling pathways or promote cytokine and chemokine secretion by immune cells or stomal cells. These inflammatory mediators provide a tumor-promoting environment that enhances AML cell survival and proliferation.

Stromal and AML cells communicate through exosomal circRNAs in the bone marrow microenvironment (63). This intercellular crosstalk influences disease progression, drug resistance and immune evasion crucial for the development of AML. Exosomes containing specific circRNAs that are secreted by AML cells can be transferred to neighboring stromal cells. For example, circRNA_100290 has been shown to be transferred from AML cells to bone marrow stromal cells. Once internalized, circRNA_100290 promotes the expression of CXCL16, which is involved in cell migration and invasion. Exosomal circRNAs adapt to the stromal-cell environment that influence their interactions with AML cells and modify the surrounding microenvironment (64). By regulating the expression or activation of specific genes or signaling pathways within stromal cells, circRNA contribute to shaping conditions that support leukemic growth (Fig. 3, top panel). In a 2023 study analyzing public AML circRNA microarray datasets (GSE94591 and GSE163386), circZBTB46 was among the most consistently upregulated circRNAs in patients with AML compared to healthy controls. Although not yet functionally characterized *in vitro* or *in vivo*, its overexpression suggests potential relevance for AML biology, warranting further studies (65).

Exosomal circRNAs as tumor biomarkers in AML. In recent years, the diagnosis of cancer has been a major focus of scientific research worldwide. Various accessible methods for the diagnosis of cancers have continued to emerge (61,66), using samples collected from tears, urine (67), semen, ascites, synovial fluid, cerebrospinal fluid, amniotic fluid (68) and feces. These sample types are easier and less invasive to obtain, and once biomarkers are detected, biopsies can be performed to analyze tumor tissues. This highlights the advantages of using exosomes as potential biomarkers. Moreover, circRNAs, as part of exosomal cargo exhibit characteristics such as structural diversity, conservation, stability and specificity in expression and localization (69).

Exosomal circRNAs have emerged as promising biomarkers as they offer several advantages, such as abundance, stability and disease specificity (69). They are considered as strong diagnostic candidates due to their differential expression in diseased AML and healthy individuals. For example, the expression of circRNA_0014130 has been shown to be high in patients with AML compared with healthy controls (25). CircRNA_0014130 has been reported to exhibit better diagnostic accuracy, with more than 90% sensitivity and specificity (25). The identification of exosomal circRNAs may help in early detection of AML resulting in timely intervention and improved patient outcomes. CircRNA_0014130 has been detected in the plasma exosomes of AML patients at early stages of disease, suggesting it to be an early diagnostic biomarker (25). These results are promising; however, multi-center validation and larger cohorts are required to confirm reproducibility and clinical applicability (70). Exosomal circ_0006896 has been shown to be upregulated in AML, and promotes proliferation, chemoresistance and immune-evasive behavior in preclinical models (71). Recent reviews and meta-analyses have provided the increasing evidence that exosomal cargo, such as circRNAs, modulates immune checkpoints and that engineered exosomes are being developed to augment immune checkpoint inhibitor and adoptive-cell therapies (72).

Studies have indicated that exosomal circRNAs may be used to monitor disease development and treatment response in patients with AML. Variations in the expression levels of specific exosomal circRNAs throughout the course of therapy can provide key insight into therapeutic efficacy and disease status (73). Monitoring circRNA levels enables the assessment of treatment response and the detection of disease recurrence (51). The isolation and detection of exosomal circRNAs from peripheral blood samples offer a minimally invasive approach for AML diagnosis and monitoring (74). Certain exosomal circRNAs exhibit prognostic value as they are associated with survival outcomes in AML patients (75). For example, circRNA_0009910 correlates with poor prognosis as higher expression levels are linked to reduced overall survival and ehanced risk of relapse (76). Exosomal circRNAs may also help in determining the treatment response and clinical outcomes in patients undergoing treatment. Expression levels of certain exosomal circRNAs is associated with disease advancement and treatment resistance in AML patients providing information related to disease severity (25). Exosomal circRNAs can also be used to monitor minimal residual disease in patients with AML following therapy, which provides information related to disease recurrence and treatment response. Patients with hepatocellular carcinoma exhibiting complete remission following chemotherapy exhibit decreased levels of circ-ITCH, suggesting its role as a predictive biomarker of the treatment response (77).

It has been demonstrated that the expression levels of certain circRNAs before treatment may determine the response to targeted therapy thereby acting as a predictive biomarker for targeted therapies. For example, it has been shown that higher levels of Circ_0059706 indicate a poor response to tyrosine kinase inhibitor (TKI) therapy and a shorter progression-free survival in AML (78,79). Exosomal circRNAs exhibit diagnostic and prognostic potential across various types of cancer. For example, the study conducted by Zheng *et al* confirmed that exosomal circRNAs derived from the serum of patients with gastric cancer served as diagnostic markers for gastric cancer (80). Exosomal circ_0072083 expression was previously shown to be upregulated in patients with glioma compared to healthy controls (81). Similarly, the dysregulated expression of exosomal hsa_circ_0064428 in hepatocellular carcinoma is associated with clinical characteristics, such as WBC count and bone marrow blast percentage (82). Elevated levels of circPAN3 have been shown to be associated with poor survival rates of patients with AML, exhibiting its prognostic significance (83). Likewise, Yan and Yan (84) reported that the overexpression of exosomal circRNA 100199 indicates severe clinical outcomes, including resistance to chemotherapy and a shorter survival duration. It has also been shown that the inhibition of exosomal circ_0072083 suppresses AML cell proliferation and induces apoptosis, highlighting its potential as a therapeutic target (29). Thus, targeting exosomal circRNAs holds considerable therapeutic promise in the management of AML (Fig. 3, bottom right panel).

Exosomal-based circular RNA delivery for AML. CircRNAs play critical roles in cancer development, including breast cancer, gastric cancer and AML. Exosomes are used as delivery vehicles for circRNAs, which exhibits a promising therapeutic strategy for the treatment of AML. Exosomes are generated through the endosomal pathway and contain biomolecules, including lipids, proteins and nucleic acids (DNA and RNA). Specific RNA motifs help in the loading of circRNAs into exosomes (73). Using motif prediction software, circRNAs with motif 5'-GMWGVWGRAG-3' were predicted to be enriched in exosomes, observed by circRNA-seq data from human blood exosomes (85). CircRNAs contribute to the pathogenesis of AML by regulating key signaling pathways and gene expression. Delivering specific circRNAs via exosomes is expected to regulate these pathways and reduce leukemic cell proliferation and survival. Exosome isolation can be achieved through several techniques, such as ultracentrifugation, size-exclusion chromatography and precipitation. Exosomes are characterized on the basis of morphology, size and protein markers, including CD9, CD63 and CD81 along with their molecular contents (86). Preclinical studies with AML animal models were used to evaluate the efficacy of exosomal circRNA delivery. These studies involve systemic administration of exosomes loaded with specific circRNAs, followed by monitoring leukemic burden, survival outcomes, and potential adverse effects. Although the therapeutic

application of exosomal circRNA delivery in AML is promising, several challenges remain, including the scalability of exosome production, optimization of loading efficiency, safety issues associated with systemic administration and the need to harness specific properties of exosomes to deliver circRNAs effectively Addressing these limitations may lead to the development of AML therapies capable of overcoming current treatment barriers and improving patient outcomes (87).

CircRNAs can be loaded into exosomes either by transfecting donor cells (e.g., mesenchymal stem cells) with circRNA-expressing plasmids or through direct loading methods such as electroporation. Transfection-based approaches allow the efficient loading of circRNAs into exosomes during their natural biogenesis within donor cells. Direct loading methods offer simplicity and flexibility, but may exhibit lower loading efficiency and can potentially alter exosomal properties. Overall, different loading techniques vary in efficiency and may have distinct downstream effects. Electroporation and donor-cell transfection are the most commonly used approaches: Optimized electroporation protocols report apparent loading efficiencies on the order of 20-35% (compared with passive incubation); however, electroporation can produce RNA precipitation artifacts and may require rigorous controls (88). Donor-cell engineering (expressing circRNA constructs or RNA-binding domain fusions) often yields higher functional loading and preserves exosome integrity (89). Once loaded with circRNAs, exosomes can be administered systemically or locally to patients with AML (90). After any loading method, EV quality control (particle count/size, TEM morphology and tetraspanin markers, such as CD9/CD63) and immune-safety testing (PBMC cytokine release, *in vivo* cytokine panels) are essential as cargo and surface modifications can alter immunogenicity (91). Exosomes possess inherent tropism toward tumor cells, including AML cells, due to the presence of specific surface proteins and ligands. Additionally, the modification of exosomal surface proteins or incorporation of targeting peptides can further enhance their specificity for AML cells. Once internalized, exosomes release their cargo including circRNAs into the cytoplasm of AML cells. These circRNAs can then exert regulatory effects; for example, circRNAs functioning as miRNA sponges can sequester oncogenic miRNAs involved in the progression of AML, while other circRNAs may modulate the expression of key AML-associated genes or signaling pathways (92). For targeted delivery to AML blasts, surface functionalization approaches directed at AML antigens (e.g., CD33) have been reported and are promising; however, preclinical data testing exosomal circRNA delivery together with standard AML drugs (cytarabine, FLT3 inhibitors) are currently limited, and combination experiments are an important future direction (93).

Exosomal circRNAs in AML metastasis. Exosomes facilitate communications between AML cells and various other cells within the microenvironment, including endothelial cells, immune cells and bone marrow stromal cells (26,92). For instance, AML-derived exosomes enriched with miR-155 have been shown to promote angiogenesis by targeting endothelial cells (94). These exosomes can enhance angiogenesis, a crucial process for tumor growth and metastasis by transporting pro-angiogenic factors, such as VEGF and FGF-2, which stimulate endothelial cell proliferation and blood vessel formation. Exosomes also play a key role in immune evasion by suppressing anti-tumor immune responses. AML-derived exosomes can carry immunosuppressive molecules, including TGF-β and PD-L1, which inhibit cytotoxic T-cell activity and thereby promote immune escape (95).

These exosomes can enhance angiogenesis, a process crucial for tumor growth and metastasis by transporting pro-angiogenic factors, such as VEGF and FGF-2, which stimulate endothelial cell proliferation and blood vessel formation. Exosomes aid in the suppression of antitumor immune responses and thus play a crucial role in immune evasion. AML-derived exosomes can carry immunosuppressive molecules, such as TGF-β and PD-L1 inhibiting cytotoxic T-cell activity and thereby promoting immune escape (96). Among these, exosomal circRNA_0056616 was shown to promote AML cell migration and proliferation by regulating the miR-625-5p/HOXA13 axis (97). The prevalence and clinical significance of these individual axes in metastatic AML remain unquantified. The majority of supporting data are derived from *in vitro* experiments, small discovery datasets, or from non-AML tumor studies; no cohort-level studies that report the proportion of patients with metastatic AML with the dysregulation of circRNA_0056616 axis have been identified (98). Metastatic AML typically signifies an advanced disease stage and a higher leukemic burden, both of which contribute to treatment resistance and reduced survival rates (99). The extramedullary manifestations of AML can also pose diagnostic challenges as their symptoms and clinical presentations may resemble those of other conditions or primary malignancies affecting the same organs (100). The accurate diagnosis of AML metastasis requires comprehensive evaluation, including imaging studies (e.g., CT scans, MRI), bone marrow biopsy, and, in some cases, tissue biopsy of the involved extramedullary site. Metastatic AML often necessitates tailored treatment approaches based on the extent and location of disease involvement. Apart from standard chemotherapy, patients with central nervous system metastasis may require intrathecal chemotherapy or cranial irradiation to control AML. Similarly, extramedullary AML lesions may require treatments, such as radiation therapy or surgical removal in combination with systemic therapy (101). AML metastasis increase the risk of post-treatment relapse, including metastasis to the central nervous system. During remission in the bone marrow, residual leukemic cells present in extramedullary sites may serve as a reservoir for relapse. Therefore, to reduce the risk of relapse strategies are to be designed to remove of prevent extramedullary disease (102). Patients with metastatic AML require close monitoring and surveillance to detect disease recurrence or progression, especially in extramedullary locations. Regular imaging and clinical assessments are critical for early relapse detection and timely intervention. Furthermore, the presence of metastatic disease may influence both the frequency and intensity of post-remission monitoring strategies. Effective symptom management and supportive care targeted toward alleviating pain, addressing neurological deficits and managing organ dysfunction remain critical components of comprehensive AML care in the metastatic setting (100).

Roles of exosomal circRNAs in AML therapy. The advantage of exosome-based therapy is their ability to mediate intercellular communication and deliver therapeutic agents to specific targets. Due to the small size of exosomes, their content is protected and thus they act as efficient therapeutic markers (103). In several studies, exosomes have shown improved therapeutic benefits in cancer treatment compared with the direct use of chemotherapeutic agents (104). Exosomes also offer potential solutions to limitations associated with current drug delivery approaches, particularly those involving programmable RNAs, which often suffer from low uptake efficiency and substantial cytotoxicity, rendering them unsuitable for clinical application (105). To address these challenges, researchers have demonstrated and validated a novel strategy for generating large quantities of RBC-derived EVs intended for RNA drug delivery (106). Furthermore, gold nanoparticle-based targeting systems have been used to engineer specific exosome types capable of precise and selective elimination of cancer cells (107-109). While exosomes containing endogenous circRNAs may contribute to cancer progression, exosomes loaded with therapeutic circRNAs or custom-engineered siRNAs against pathogenic circRNAs hold considerable promise for inhibiting tumor growth. Delivering circRNAs that suppress cancer hallmarks and promote apoptosis may further enhance the development of precise, effective therapeutic strategies (110).

Exosomal circRNAs affect treatment response by regulating processes such as drug resistance, apoptosis and immune evasion and thus have emerged as important regulators of therapeutic responses in AML. CircRNA_000911 has been implicated in chemoresistance in by sponging miR-449a and upregulating HDAC1, which reduces apoptosis and promotes cell survival (111). CircRNAs may also regulate drug efflux pump encoding genes that leads to alteration in the intracellular concentration of chemotherapeutic agents and thus contributes to resistance. Exosomal circRNAs can also regulate apoptosis-related pathways affecting sensitivity of AML cells to treatment-induced cell death. Moreover, exosomal circRNAs play critical roles in the response to targeted therapies in AML, including genetically targeted drugs and TKIs. By regulating the expression of pro- or anti-apoptotic genes, circRNAs can shift the balance between cell survival and apoptosis (68). For instance, circRNA_0004015 promotes resistance to TKI therapy by upregulating anti-apoptotic proteins and suppressing chemotherapy-induced apoptosis (112). The overexpression of such circRNAs can enhance immune evasion and tumor progression by inhibiting T-cell activation and cytokine secretion (76).

Exosomal circRNAs can regulate molecular pathways that affect drug metabolism, cell survival and apoptosis thereby influencing the efficacy of targeted therapies (29). They also modulate the expression of genes encoding drug targets or signaling molecules involved in precision therapy (75). Additionally, exosomal circRNAs can alter drug metabolism and pharmacokinetics by affecting intracellular uptake and bioavailability. For example, circPAN3 has been shown to be associated with development of AML drug resistance doxorubicin through regulating autophagy (83). Exosomal circRNAs may serve as predictive biomarkers of treatment resistance and disease relapse. Reduced intracellular drug accumulation and decreased sensitivity to chemotherapeutic agents (25), combined with treatment-induced changes in circRNA expression, can indicate the emergence of resistant clones and the need for alternative therapeutic strategies. Integrating exosomal circRNA profiles with clinical parameters, such as cytogenetics, molecular mutations and patient demographics significantly enhances their predictive value. Multivariate analyses incorporating circRNA levels and conventional prognostic factors have yielded improved risk stratification and more accurate assessments of the treatment response (113). For instance, the increased expression of circ_100053 enhances CML cell resistance to cytarabine by promoting proliferation and inhibiting apoptosis (48).

Exosomal circRNAs may also regulate gene expression programs involved in AML progression and therapy response (75). Certain circRNAs, such as circ-foxo3 and circ-0004277, exhibit an altered expression in *de novo* AML and are associated with disease characteristics (51). Their stability renders exosomal circRNAs attractive candidates for reliable diagnostic biomarkers that support early detection and disease monitoring. Identifying exosomal circRNAs involved in the pathogenesis of AML may also reveal therapeutic opportunities aimed at targeting their expression or function. Furthermore, exosomal circRNAs can exert immunomodulatory effects, influencing interactions between AML cells and the immune system. Understanding these associations may have key implications for AML immunotherapy strategies (116) (Fig. 3, bottom left panel).

4. Prospects and challenges of exosomal circRNA in AML

Advanced molecular profiling that identifies the various mutations and molecular aberrations driving AML pathogenesis has paved the way for targeted therapies. Specific drugs that target key mutations, such as FLT3 inhibitors (e.g., gilteritinib and midostaurin) and isocitrate dehydrogenase (IDH) inhibitors have already demonstrated promising outcomes in clinical trials. Immunotherapeutic approaches, combined with the integration of transcriptomic, genomic, and proteomic data, are enabling more individualized treatment strategies in AML. Therapies tailored to the mutational profile and risk stratification of each patient hold significant potential for optimizing treatment outcomes. Ongoing research into novel agents, including differentiation-inducing compounds, epigenetic modifiers, and emerging targeted therapies, continues to open new avenues for the management of AML. Combination therapies targeting multiple pathways simultaneously are also being explored to overcome drug resistance and improve response rates (115).

One of the major challenges in AML is the development of treatment resistance, which contributes to disease relapse and poor outcomes. Resistance mechanisms, such as clonal evolution, tumor heterogeneity and the activation of alternative signaling pathways require the development of innovative therapeutic strategies. Although targeted therapies have shown benefit in specific AML subgroups, a number of patients either lack actionable mutations or eventually develop resistance (116). Identifying additional druggable targets and developing rational combination therapies are essential for improving treatment responses in these patients. The

significant molecular and phenotypic heterogeneity observed among patients with AML contributes to variable therapeutic responses and clinical outcomes. evolution and the emergence of subclones with distinct genetic alterations further complicate treatment planning and disease monitoring. Moreover, intensive chemotherapy regimens commonly used in AML are associated with substantial toxicity, including myelosuppression, infection, and organ damage. Balancing therapeutic efficacy with effective toxicity management therefore remains a major clinical challenge (116).

5. Conclusions and future perspectives

Exosomal circRNAs have emerged as key players in the pathogenesis of AML. Encapsulated within exosomes, these circRNA molecules exhibit regulatory functions in AML progression and hold potential implications for diagnosis, prognosis, and therapy. Exosomal circRNAs participate in various cellular processes and play vital roles in the Clonal development of AML, including proliferation, apoptosis evasion, drug resistance and metastasis. They also serve as non-invasive biomarkers for AML diagnosis. Their stability in body fluids, such as urine and blood, along with their dysregulated expression patterns in patients with AML, renders them attractive candidates for early detection and disease monitoring. Clinical studies have linked specific exosomal circRNA expression profiles with patient outcomes. High expression levels of particular circRNAs are associated with adverse prognostic factors, including chemotherapy resistance, disease relapse and a poor overall survival. Targeting exosomal circRNAs represents a novel therapeutic strategy in AML management; modulating their expression could potentially restore normal cellular processes, overcome drug resistance and improve treatment efficacy. Despite their promise, the clinical application of exosomal circRNAs faces several challenges, including the need for standardized isolation and detection techniques, clarification of their precise molecular mechanisms, and validation of their therapeutic utility in large patient cohorts. The selection of the exosome isolation method substantially affects downstream circRNA recovery and assay specificity. For plasma-based AML biomarker work, it is generally recommended to use ultrafiltration (UF) followed by size-exclusion chromatography (SEC) as SEC provides superior removal of abundant plasma protein and lipoprotein contaminants while preserving intact vesicles and RNA suitable for qPCR and RNA-seq. Single-step precipitation methods yield higher apparent particle/RNA yield but poor purity and are not suitable for clinical validation. Future research is warranted to focus on addressing the challenges that limit the full potential of exosomal circRNAs in AML diagnosis and therapy. All clinical validation studies should follow MISEV2018 reporting, include pre-analytical SOPs (double-spin plasma, hemolysis checks, storage at -80˚C), and report EV QC metrics (NTA/TEM, CD9/CD63/CD81, negative markers) (59).

To address existing gaps in the literature, the present review primarily focused on the role of circRNAs in AML and discussed their potential in disease management. This includes their contributions to leukemogenesis and drug resistance, as well as their promise as novel diagnostic, therapeutic and prognostic biomarkers. The present review also discussed the involvement of exosomal circRNAs, providing a deeper perspective on the genetic mechanisms underlying AML, which may open new avenues for targeted therapy. Furthermore, future studies are warranted to translate these findings into clinical applications in order to improve the diagnosis and management of patients with AML.

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Authors' contributions

SK conceptualized the study. THA, PKT, MS, SKM and AMSU were involved in the writing and preparation of the original draft of the manuscript. THA, RM and MS were involved in the writing, review and editing of the manuscript. PKT, THA and SK were involved in visualization. SK supervised the study. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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