

The regulatory role of exosomes in leukemia and their clinical significance

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Abstract

Recurrence is a primary cause of death in patients with leukemia. The interactions of tumor cells with the microenvironment and tumor stem cells hidden in bone marrow promote the recurrence and metastasis of leukemia to lymphoid tissue. Exosomes, membrane-coated nanovesicles secreted by living cells, perform biomaterial transfer and information exchange between cells. Exosomes contain various other biological components derived from parental cells, and they remotely regulate the function of target cells through body fluid flow. Recent studies revealed that exosomes participate in the development of leukemia and play important roles in its diagnosis and treatment by influencing cell proliferation and apoptosis, regulating bone marrow microenvironment, promoting angiogenesis, and inhibiting hematopoiesis. Exosomes are potential biomarkers and therapeutic targets for leukemia, and they can influence drug resistance. Leukemia-derived exosomes present leukemia-related antigens to target cells, promote the proliferation of leukemic cells, help these cells escape immunity, protect them from the cytotoxic effects of chemotherapeutics, and promote angiogenesis and tumor migration. Therefore, exosomes are closely related to the metastasis, treatment, and prognosis of leukemia, and they can be used to detect and monitor the progression of leukemia. This paper reviews the regulatory roles of exosomes in leukemia and their clinical significance.

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Keywords

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Introduction

Leukemia is a malignant clonal disease originated from bone marrow hematopoietic stem cells, including chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), and acute lymphocytic leukemia (ALL).¹ Among them, acute leukemia accounts for two-thirds of all cases of leukemia, and it is the leading cause of cancer-related death in children and adults younger than 35 years old with a rather low recovery rate. With the improvement of chemotherapy and the progression of hematopoietic stem cell transplantation, the remission rate has been reduced. However, most patients still experience relapse after remission, and the overall 5-year survival rate is only 40% to 50%.² Therefore, it is extremely important to understand the causes of leukemia, the condition of metastasis, and the causes of relapse.

Exosomes are lipid bilayer membrane vesicles with a diameter of 30 to 150 nm, and they contain RNAs, proteins, microRNAs, DNA fragments, and other components.³ Exosomes can be produced by most types of cells, such as mast cells, tumor cells, dendritic cells, neurons, and astrocytes. In body fluids, exosomes exist in plasma, urine, ascites, lymph, and cerebrospinal fluid. Exosomes play important physiological and pathological roles via communication with adjacent cells and distant target cells.⁴ They can mediate information and biomaterial exchange between different cells at a certain distance through the transfer of proteins, DNA, RNA, and microRNA. They also participate in the

processes of immune response, antigen presentation, migration, differentiation, and invasion of tumor cells.⁵ In recent years, increasing attention has been paid to the unique role of exosomes in tumor metastasis and the response to chemotherapy. Exosomes are closely related to the survival, proliferation, metastasis, and recurrence of tumors, and they play an important role in the diagnosis and pathological identification of tumors and provide new avenues for immunotherapy.

The formation and release of exosomes

The formation of exosomes is a continuous process.⁶ First, extracellular materials or membrane proteins are internalized to form early endosomes, which gradually mature into late endosomes through intracellular transportation. Under certain physiological and pathological conditions, the boundary membrane of late endosomes is sunken inward at many sites, forming multivesicular bodies (MVBs). More than 20 types of vesicular sorting proteins are involved in the formation of MVBs, among which the most important types are four types of endosomal sorting complexes required for transport (ESCRTs) and vacuolar protein sorting 4 (VPS4). MVBs can both fuse with lysosomes and release degraded contents from cells and form intraluminal vesicles via inward budding, and these vesicles can fuse directly with cell membranes, fall off with the help of ESCRT III, undergo release into the extracellular environment, and form exosomes. Exosomes released into the intercellular substance will enter receptor cells through

endocytosis or a ligand-receptor recognition process and participate in signal transmission after the “goods” are released into the cytoplasm of receptor cells. Contrarily, they can re-form MVBs or fuse with the plasma membrane directly for the next cycle.

The isolation and identification of exosomes

The common methods for exosome separation are differential centrifugation, sucrose density gradient ultracentrifugation, immunoprecipitation, and exosome extraction using commercial kits. Each method has its own advantages and disadvantages.⁷ At present, there is no uniform standard for the separation or extraction of exosomes. The separation and identification mainly depend on whether the purity of the extracted exosomes can be ensured, excessive heteroproteins can be avoided, and the known protein markers of exosomes can be identified. Only the extraction of exosomes with high purity, yields, and concentrations can ensure the quality of subsequent research. Currently, several techniques are available for identifying exosomes. In addition to the commonly used techniques transmission electron microscopy, particle size detection, and flow cytometry, atomic microscopy, electron microscopy, dynamic light scattering technology, and biological immune technology have also been used.⁸ Although exosomes derived from cancer cells/tissues have great potential for the early diagnosis of cancer, their clinical potential has not been fully explored because of the lack of cost-effective multiplex approaches capable of effectively isolating and identifying specific exosome populations and analyzing their biomarker content. A recent study developed paper-based isotachopheresis technology capable of the 1) rapid isolation and identification of exosomes from both malignant and

healthy cells and 2) multiplex detection of selected exosomal protein biomarkers of the target exosomes, exhibiting promising clinical value.⁹

Exosomes in four types of leukemia

Exosomes in AML AML is a malignant hematological system disease in which the differentiation of hematopoietic stem cells or progenitor cells is blocked and cell proliferation is disordered. A recent study confirmed that AML can reconstruct the bone marrow microenvironment into one that promotes the growth of leukemia cells but inhibits normal hematopoietic function by secreting exosomes. AML-derived exosomes can inhibit the expression of the hematopoietic factor DKK1 and induce the downregulation of hematopoietic stem cell promoters in bone marrow stromal cells, creating a favorable microenvironment for the proliferation and survival of leukemia cells.¹⁰ AML exosomes can also promote the survival of healthy hematopoietic stem cells and induce leukemia-like functional features, leading to the overexpression of miR-21 and miR-29.¹¹ Exosomes both play an important role in the construction of the tumor microenvironment and mediate information transfer between stem cells and tumor cells. Leukemia stem cell-derived exosomes were found to promote the proliferation and migration of AML cells and inhibit their apoptosis.

Exosomes in CML Exosomes derived from CML cells can be accumulated by endothelial cells and promote endothelial cell tube formation. Exosomes from K562 cells induced dasatinib-sensitive Src phosphorylation and the activation of downstream Src pathway proteins in endothelial cells. Dasatinib may have greater activity than imatinib because of the involvement of Src in both leukemia cells and the

angiogenic microenvironment.¹² In addition, CML exosomes can establish an auto-crine loop with their parent cells through a ligand–receptor interaction mediated by exosome-associated transforming growth factor (TGF)- β 1, followed by the activation of extracellular signal-regulated kinase, protein kinase B, and nuclear factor (NF)- κ B signaling, leading to increased CML cell proliferation and survival.¹³

Exosomes in ALL. ALL is the main type of pediatric leukemia, and it carries a high cure rate. However, children must undergo repeated bone marrow biopsies. Both primary ALL and the corresponding cell lines release large vesicles with membrane structures containing complete organelles and a cytoskeleton, which are important mediators of intercellular communication. Based on the actin structure in ALL-derived exosomes, researchers established a technique for tracking ALL-derived exosomes in the blood of patients, providing a novel method for diagnosis, treatment, and analgesia in children with ALL.¹⁴

Exosomes in CLL. Exosomes play a key role in the communication between CLL B cells and the bone marrow microenvironment. CLL-derived exosomes were found to regulate the tumor microenvironment by regulating Akt signaling and inducing the high expression of CLL promoters such as VEGF.¹⁵ Conversely, bone marrow stromal cell-derived exosomes can enhance the migration and chemotherapeutic resistance of CLL B cells and help CLL cells escape spontaneous or drug-induced apoptosis. CLL exosomes are also involved in immune regulation in patients with tumor. There are greater numbers of PD-L1 receptors on the surface of monocytes and macrophages in mice with CLL, and the deriving exosome RNA promotes the expression of PD-L1 in patients with CLL; thus, regulating PD-L1 provides a

new immunotherapeutic strategy for CLL.¹⁶ Researchers have conducted deep research into exosomes as CLL biomarkers. CD19, CD37, and CD52 exosomes and miRNA155 are good indicators of CLL clinical staging and drug guidance. Exosomes containing CLL transcripts can also transfer the related miRNAs to healthy mesenchymal stromal cells, leading to malignant proliferation.

The regulatory effects of exosomes on leukemia

Exosomes and the survival and proliferation of leukemia. The “carcinogenic” information in leukemia cells is internalized by neighboring cells via the transporters and RNAs carried on exosomes, and this information is transported to distant cells via fluid flow. Exosomes from AML cells are rich in nucleic acid information, which can promote leukemia progression. In a CML xenograft model, the treatment of mice with exosomes induced a greater increase in tumor size compared with the findings in controls.¹³ An increase in the mRNA and protein levels of anti-apoptotic molecules and a reduction in the levels of pro-apoptotic molecules were observed.¹³ This finding suggests that CML-derived exosomes promote, through an autocrine mechanism, the proliferation and survival of tumor cells, both *in vitro* and *in vivo*, by activating anti-apoptotic pathways. Leukemia and stromal cells have also been found to establish bidirectional crosstalk; specifically, exosomes promote the proliferation and survival of leukemia cells, both *in vitro* and *in vivo*, by inducing IL8 secretion from stromal cells.¹⁷ Human T lymphocyte virus type I (HTLV-I) is one of the main causes of adult T cell leukemia. T cells infected by HTLV-I release exosomes carrying Tax and its mRNA.¹⁸ In addition, exosomes can improve cell viability by enhancing the phosphorylation of AKT

and RB in mouse and human T cell lines and inhibit Fas-mediated Jurkat cell apoptosis by increasing the activities of cFLIP and NF- κ B,¹⁹ suggesting that leukemia cell-derived exosomes promote the development of leukemia and play a positive role in regulating the survival and proliferation of leukemia cells.²⁰

The regulatory role of exosomes in the bone marrow microenvironment. The critical pathogenesis of AML involves the creation of a bone marrow microenvironment supporting the formation and progression of leukemia cells. AML derived-exosomes are rich in specific coding and non-coding RNAs, which are closely related to the pathogenesis of AML. AML exosomes can be absorbed by bone marrow stromal cells, and they transport specific RNAs, downregulate the expression of genes related to hematopoietic regulation such as SCF and CXCL12 in stromal cells, decrease the colony-forming ability of hematopoietic stem progenitor cells, inhibit hematopoietic transcription factors, and thus suppress the normal hematopoietic function of bone marrow.²¹

CLL is a low-grade malignant small lymphocyte clonal disease that is characterized by the accumulation of large numbers of monoclonal lymphocytes in peripheral blood and their infiltration into the liver, spleen, lymph nodes, and other organs. Abnormalities in migration, proliferation, survival, and apoptosis in CLL cells can be induced through direct contact between the tumor microenvironment and tumor cells or the indirect action of soluble factors, resulting in CLL pathogenesis. The interaction between CLL cells and the microenvironment is regulated by the B cell receptor signaling pathway, which affects the survival, proliferation, adhesion, migration, and drug resistance of CLL cells. A recent study²² found that stimulation with α -IgM increased the release of miR-

155-rich CLL exosomes, whereas ibrutinib, a Bruton tyrosine kinase inhibitor, inhibited the α -IgM-stimulated release of CLL exosomes, confirming the close relationship between miR-155 and B cell receptor signaling. CLL-derived exosomes were found to bind to bone marrow mesenchymal stem cells (BMSCs) and endothelial cells, transfer functional proteins and miRNAs to target cells, regulate NF- κ B signaling for kinase activation and the activity of transcription factors, influence gene expression, transform stromal cells into tumor-related fibroblast-like phenotypes, promote the proliferation, cytoskeleton reconstruction and migration of CLL cells, improve the bone marrow microenvironment, and promote tumor progression.²³

Exosomes promote angiogenesis in leukemia.

Neovascularization is an indispensable step in the development of malignant tumors, especially for tumors larger than 1 to 2 mm. Exosomes have been demonstrated to play an intermediate role during neovascularization.²⁴ CML-derived exosomes induce human umbilical vein endothelial cells (HUVECs) to form vascular-like tubular structures by transporting miR-92a and activating Src signaling. Umezue et al.²⁵ were the first to report leukemia cell to endothelial cell communication via exosomal miRNA, which may contribute to increased angiogenesis in leukemia, by illustrating that Cy3-labeled pre-miR-92a was transferred into the cytoplasm of HUVECs and that the Cy3 signal colocalized with the exosomal marker CD63. Additionally, they treated K562/Cy3-miR-92a cells with the neutral sphingomyelinase inhibitor GW4869²⁶ and isolated exosomes from the cultured cells, which were then cocultured with HUVECs. HUVECs did not display a Cy3-miR-92a signal, suggesting that GW4869 blocked exosome miRNAs secretion by inhibiting ceramide biosynthesis.²⁵ Endothelial cells exhibited increased

angiogenesis properties upon the incorporation of leukemic exosomes.²³ These results indicate that leukemia cells release exosomes containing angiogenic factors and transfer them to endothelial cells, creating a favorable microenvironment for angiogenesis.

Exosomes inhibit hematopoiesis in leukemia. A recent study found that AML-derived exosomes exerted a direct inhibitory effect on hematopoietic stem/progenitor cells (HSPCs).²⁷ High levels of miR-150 and miR-155 were found in exosomes extracted from AML cells and the plasma of nude mice subjected to AML transplantation. In the co-culture of plasma exosomes and HSPCs, exosome-derived miR-150 and miR-155 could inhibit the translation of c-MYB-encoded transcription products involved in HSPC differentiation and proliferation, block colony formation, and thus suppress hematopoiesis.²⁷ Exosomes can also be function as paracrine regulators in the tumor microenvironment. In AML mouse models, exosomes affected hematopoietic function by downregulating the key maintenance factors SCF and CXCL12 in hematopoietic stem cells in the stroma, suggesting that AML exosomes participate in the suppression of residual hematopoietic function that precedes widespread leukemic invasion of the bone marrow directly and indirectly via stromal components.²¹

Exosomes and immune escape. In recent years, exosomes have been found to play important roles in immune escape, cell proliferation, chemoresistance, and the diagnosis and prognosis of leukemia.²⁸ Exosomes from acute T-cell leukemia cells and lymphoma cells contain MICA/B and ULBP1/2, which can bind with NKG2D in natural killer (NK) cells and further block the binding of NKG2D with ligands on the leukemia cell membrane, thereby reducing the ability of NK cells to kill

leukemia cells.²⁹ Under tumor hyperthermia and oxidative stress, the release of T cell/B cell leukemia and lymphoma cell-derived exosomes increases, and the immunosuppressive effect of NK cells is enhanced. Leukemia cell-derived exosomes promote the development of leukemia and play a positive role in the survival and proliferation of leukemia cells. Leukemic exosomes can transfer antigens to dendritic cells (DCs) and play an anti-tumor role. Contrarily, exosomes released by DCs can induce immune responses. A prior study³⁰ reported that after silencing TGF- β 1 in exosomes derived from mouse lymphocytic leukemia, a DC vaccine prepared using the obtained exosomes can promote the proliferation of CD4⁺ T cells and the secretion of Th1 cytokines, induce antigen-specific CTL responses, inhibit the tumor growth, and prolong survival in mice.

Exosomes as drug carriers for leukemia

Exosomes display tissue specificity. According to the differential expression of surface molecules, exosomes can target specific cells as carriers to deliver therapeutic agents. For example, exosomes can transport drugs that inhibit the BCR-ABL fusion protein and specifically target IL3-R. Another study demonstrated that IL3L exosomes loaded with imatinib or BCR-ABL siRNA could target CML cells and inhibit cancer cell growth *in vitro* and *in vivo*.³¹ Many studies revealed that drugs affect the development of leukemia by acting in concert with exosomes. Curcumin, with its anti-tumor effect, inhibits angiogenesis by upregulating exosome-derived miR-21 shuttling into endothelial cells. This agent also reduced angiogenesis by suppressing the effect of exosomes on angiogenesis and regulating the endothelial barrier.³² All-trans retinoic acid was found to change the production characteristics of extracellular vesicles (EVs) related to NB4

cells in the treatment of acute promyelocytic leukemia.³³ This treatment also increased the expression of IL8 mRNA and protein in NB4 cells and their EVs, reduced VEGF and tissue factor levels, and suppressed EV-related angiogenesis activity released by NB4 cells. Studies also illustrated that exosomes with low expression of TGF- β 1 could target dendritic cells, promote their maturation, and induce effective anti-leukemia immunity.³⁰ This type of targeting effect is expected to become a new immunotherapeutic strategy for leukemia. EVs secreted by activated human NK cells can exert cytotoxic effects on cancer cells by activating the caspase pathway in target cells and play an important role in tumor immunity. Exosomes can also target IL3- γ to inhibit the growth of CML cells.³¹

Exosomes as biomarkers for leukemia

Regarding the advantages of exosomes carrying biological substances, exosome-derived miRNAs are not degraded by extracellular ribonuclease, making exosomes a repeatable and consistent biomarker.³⁴ Studies have found that exosomes, especially their microRNAs, can exist stably and substantially in many body fluids, such as blood and urine.³⁵ The types and expression levels of specific proteins and microRNAs in exosomes are found to be closely related to diseases. Exosomes from pathological cells exhibit similar miRNA expression profiles as the parental cells; therefore, it is possible to collect body fluids and analyze the pathology under non-invasive condition to monitor disease progression.³⁶ Exosomes thus can be used as non-invasive biomarkers. A study using DotScan antibody microarray analyzed the surface of exosomes extracted from the culture medium of cancer cells and the plasma of patients with CLL to monitor the occurrence of cancer and dynamically observe the change of patients'

conditions.³⁷ In addition, the changes of protein and/or TGF- β 1 levels in exosomes may reflect the response of patients with AML to chemotherapy, and the presence of plasma exosomes may reflect the presence of residual lesions in patients with complete remission. Low exosome levels after treatment indicate long-term disease-free survival. As a marker of the efficacy of chemotherapy in patients with AML, plasma exosomes can also be used as a biomarker to monitor the relapse of leukemia.³⁸ The interplay between BMSCs and AML plays a critical role in AML drug resistance by secreting growth factors, cytokines, and EVs. A prior study illustrated that exosomes secreted by AML cells serve as essential communicators for the interaction of BMSCs and AML, which can protect AML cells against chemotherapy-induced apoptosis.³⁹ CML is characterized by the Philadelphia chromosome, which involves a translocation between chromosomes 9 and 22. The resultant BCR-ABL1 fusion gene encodes a protein with constitutive tyrosine kinase activity. Studies have found that monitoring BCR-ABL1 transcript levels in patients undergoing treatment with tyrosine kinase inhibitors is considered the standard of care for patients with CML and is critical for appropriate therapy selection.^{40,41}

Exosomes and the diagnosis of leukemia

In hematological malignancies, a study found that the exosomal expression of TGF- β in patients with AML was significantly higher than that in healthy people. After chemotherapy, TGF- β levels were dramatically decreased. After long-term and complete remission, TGF- β levels are extremely low, suggesting that exosomes from AML can be used as a potential diagnostic marker. Another study that EV levels in the peripheral blood of patients with AML at three different stages (initial diagnosis, neutropenia, and remission) were

significantly higher than those in patients with complete remission and healthy controls,⁴² suggesting that EV levels can be used as an indicator for the diagnosis of minimal residual diseases.

Exosomes and the prognosis of leukemia

In a study of hematological malignancies, miR-155 levels in microparticles might be a risk marker for the transition of monoclonal B lymphocytosis to CLL and a potential pre-post marker for patients with CLL.⁴³ In addition, CD44 in serum EVs from patients with multiple myeloma (MM) was identified as a potential marker for evaluating overall survival.⁴⁴ The differential expression of certain exosome miRNAs has been proven in high-risk and low-risk patients with MM, suggesting that exosomal miRNA can be used as a potential prognostic indicator.

Discussion

At present, exosomes and exosome-derived miRNAs have been recognized as intracellular signal transducers. During the progression of leukemia, exosomes secreted by leukemia cells can promote the development of leukemia by influencing the proliferation and apoptosis of leukemia cells, regulating the bone marrow microenvironment, influencing angiogenesis, and inhibiting hematopoiesis. Exosomes can also be used as biomarkers for leukemia to monitor the occurrence and progression of leukemia.⁴⁵ It has been confirmed that exosomes can be used in the treatment of leukemia by transporting therapeutic drugs or inhibiting the exosome-involved development of leukemia. However, the underlying mechanism remains unclear, and current research is mainly using cell lines or leukemia mouse models to reveal the participation of exosomes in the treatment of leukemia. Further studies should focus on the

mechanism and signaling pathways of exosomes in the treatment of multiple leukemia cell lines. The recurrence of leukemia is a major problem in the clinical treatment of leukemia. Exosomes have been reported to be involved in the regulation of drug resistance in leukemia. However, our understanding of the mechanism of drug resistance and targeted therapy involving exosomes in leukemia is relatively low. The study of exosomes and their miRNAs in drug resistance mechanism and the targeted treatment of leukemia represent new research areas. In conclusion, exosomes represent a potential mediator in the diagnosis, treatment, and monitoring of leukemia; however, more efforts should be made to achieve its clinical use.⁴⁶ We should make full use of basic clinical models such as leukemia cell lines and leukemia mouse models to study the specific mechanism, signaling pathways, and negative feedback mechanisms of exosomes in the pathogenesis, treatment, and drug resistance of leukemia, which would provide novel directions for the use of exosomes in the clinical treatment of leukemia.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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