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REVIEW

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Harnessing the power of exosomes for diagnosis, prognosis, and treatment of hematological malignancies

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Abstract

Exosomes are small extracellular vesicles of endocytic origin released by various cell types. They consist of lipid bilayers containing macromolecules such as lipids, proteins, microRNAs, growth factors, cytokines, and carbohydrates. Exosomes play a critical role in the diagnosis and treatment of various diseases. For instance, exosome contents have been utilized as biomarkers in body fluids (urine, saliva, serum) to identify cancers, autoimmune diseases, and inflammatory conditions such as sepsis. Due to their small size and ability to reach tumor microenvironments, exosomes are also used as carriers for chemotherapeutic drugs in drug delivery systems. Furthermore, evidence indicates that malignant cells release exosomes into the tumor microenvironment, influencing immune cells in a paracrine manner. Additionally, immune cell-derived exosomes, such as those from Natural Killer (NK) cells or cytotoxic T lymphocytes (CTLs), show potential as therapeutic agents in treating malignancies like leukemia. This review discusses the diagnostic role of exosomes in various hematological malignancies and explores the therapeutic potential of immune cell-derived exosomes in these diseases.

Keywords Small extracellular vesicles, Exosomes, Stem cell, MicroRNAs, Hematological malignancies

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Introduction

Hematological malignancies, which comprise a diverse array of diseases, include leukemia, multiple myeloma (MM), myelodysplastic syndromes (MDS), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL), are characterized by the disruption of the production and function of myeloid and lymphoid cell lines [1–3]. Hematopoietic stem cell transplantation (HSCT) and chemotherapy represent the primary treatment strategies for most hematological malignancies. Despite these interventions, disease relapse and drug resistance remain significant challenges, with a reported 5-year survival rate of only 40–50% [4]. One major factor contributing to resistance and relapse is the persistence of leukemic stem cells (LSCs) within the bone marrow niche. These LSCs evade treatment, receive signals necessary for self-renewal, and adversely affect healthy hematopoietic stem cells [5]. In recent years, exosomes have emerged as critical players in cell-cell communication and therapy resistance across various malignancies. These small extracellular vesicles facilitate the proliferation and invasiveness of recipient cells, as well as contribute to drug resistance [6]. Exosomes are integral to numerous biological pathways and serve as key mediators of intercellular communication in both physiological and pathological contexts. Secreted by diverse cell types, exosomes participate in a wide array of processes. Due to their involvement in pathological conditions, there is ongoing research to exploit exosomes as therapeutic agents by loading them with proteins, microRNAs (miRNAs), and chemotherapeutic agents [7, 8].

Moreover, exosomes have been reported to modulate both innate and adaptive immune responses. Various immune cells, including dendritic cells (DCs) and B and T lymphocytes, secrete exosomes that exhibit immune-modulating properties and are detectable in body fluids [9, 10]. Additionally, tumor cell-derived exosomes can present tumor antigens to DCs, thereby stimulating antitumoral immune responses [11, 12]. However, the effects of tumor-derived exosomes are complex and sometimes controversial, as they can either promote antitumoral responses or exert immunosuppressive effects. Some studies indicate that exosomes suppress immune responses by inhibiting T lymphocyte proliferation and natural killer cell activity, or by promoting the development of immunosuppressive cells, such as regulatory T cells or myeloid-derived suppressor cells [13–18]. Building on these insights, this review aims to elucidate novel aspects of hematological malignancies by focusing on the role of exosomes in the interplay between malignant cells and the bone marrow niche, as well as their contribution to disease resistance and relapse. We also explore the potential therapeutic applications of exosomes in treating hematological malignancies.

Exosomes in hematological malignancies

Content of leukemic exosomes

Leukemia-derived exosomes are small vesicles, 30–150 nm in diameter, released by leukemic cells that play a crucial role in leukemia progression [19]. These exosomes contain diverse substances, including proteins, lipids, microRNAs (miRNAs), and nucleic acids, which can be transferred to other cells in the body, thereby altering their function [19, 20].

In patients with acute myeloid leukemia (AML), miRNAs are notably enriched in cell-derived exosomes. These exosomes contain nine components related to hematopoiesis and leukemogenesis, as well as five potential biomarkers for AML prognosis, indicating their critical role in disease monitoring and management [19]. Additionally, significant increases in miRNAs such as *let-7a*, *miR-9*, *miR-99b*, *miR-150*, *miR-155*, *miR-191*, and *miR-223* have been observed in AML cell-derived exosomes, with levels ranging from two to forty times higher than those in the parent cells (Table 1) [21]. The specific miRNAs mentioned play important roles in acute myeloid leukemia (AML). *Let-7a* acts as a tumor suppressor, playing a key role in regulating cell proliferation and differentiation. Its presence is associated with improved prognosis in AML patients [22, 23]. *miR-9* plays a crucial role in regulating cell differentiation and proliferation, processes that are fundamental in the development of various cancers. Similarly, *miR-99b*, which belongs to the *miR-99* cluster, is involved in the regulation and differentiation of hematopoietic stem cells. It also contributes to cell proliferation during the differentiation of megakaryocytes, neutrophils, and monocytes, highlighting its significance in hematopoiesis [24]. *miR-150* is primarily recognized for its role in regulating B-cell differentiation and has been linked to various hematological malignancies. On the other hand, *miR-155* functions as an oncogene in AML, with elevated levels correlating with a poorer prognosis. Beyond its role in leukemia, *miR-155* is also a key regulator of immune responses and inflammation, further emphasizing its importance in disease progression and the immune environment (Table 1) [23, 25, 26]. *miR-191* is widely recognized for its role in regulating the cell cycle and has been implicated in the development of several cancers. Meanwhile, *miR-223* exhibits a dual nature, functioning as either a tumor suppressor or an oncogene depending on the biological context. It plays a crucial role in granulocytic differentiation and shows increased expression during retinoic acid-induced differentiation in AML, underscoring its significance in leukemia biology [22, 25, 26]. This suggests a potential mechanism through which exosomes contribute to leukemia progression by enhancing the expression of these miRNAs in recipient cells. Furthermore, B-cell acute lymphoblastic leukemia (B-ALL) cells release exosomes containing interleukin-15

Table 1 Exosome cargos and their function in tumor progression

Cancer Type	Targets	Function	References
AML	TGF-β1 MICA, MICB, ULBP1, ULBP2, BAG6	Decrease the effectiveness of natural killer (NK) cells in targeting leukemic cells	[231, 232]
	GATA1, FOX3, SHIP1, ID1, E2F1, CEBP-α, Myc	Initiate the progression of leukemia	[233]
	miR-20a, miR-196	- Expelled specific RNAs from cells. (These specific RNAs were detrimental to the survival of tumors)	[234]
	ABCA3	Membrane structures serve as a confinement for anti-tumor medications	[235]
	IGF-IR, mRNA, MMP9	- Enhanced stromal cell proliferation - Promoted stromal cell release of growth factors	[236]
	IL-10, TGF-b	The promotion of the conversion of CD4 + CD25 – T cells into Treg cells	[237]
	FasL, PD-L1, TGF-b	The suppression of Immune cells fighting tumor growth	[60, 238, 239]
ALL	Galectin-3, NF-kB	Advocate for broad-spectrum drug resistance	[63]
	P-gp	Encapsulated anti-cancer medications within membranous formations	[240]
CLL	Y RNA hY4	Monocytes were prompted to adopt an immunosuppressive phenotype	[241]
	miR-21, miR-146a, miR-150, miR-155, S100-A9	- Enhanced MSC proliferation, EC angiogenic activity, CLL cell survival, and proliferation are observed. - The presence of drug resistance is noted. - The activation of the NF-kB pathway is associated with leukemia progression.	[242–244]
CML	SRC, TSP-1, IL-8, miR-210	- Enhances the formation of new blood vessels by endothelial cells - Boosts the vascular function of chronic myeloid leukemia	[86]
	miR-92a, miR-365	- Enhanced formation of vascular tubular networks - Inhibited expression of Caspase3 and apoptosis of tumor cells	[245, 246]
	hTERT mRNA	- Fibroblast transition into cancer-associated fibroblasts (CAFs) can improve the survival of leukemia cells. - This transition process plays a crucial role in supporting cancer cell growth and progression.	[247]
	BCR-ABL1 mRNA	BM-MSC were prompted to develop a tumor-supportive characteristics	[248, 249]
	Amphiregulin	Activation of EGFR signaling in stromal cells results in an upregulation of IL-8 expression	[236, 250]
	MAC	MAC eradication in cancer cells	[251]
	TGF-b	Improved the viability and proliferation of cancerous cells	[248]
	PI3/AKT, MAPK/ERK, NF-kB, TGF-α1	Improve the viability of LAMA84 cells	[252]
MM	IL-6, CCL2, fibronectin	MM cells proliferation is fostered by enhancing survival, expansion, and migration of tumor cells	[253, 254]
	miR-135b	Downregulation of FIH-1, upregulation of HIF-1 bioactivity, and stimulation of angiogenesis facilitate the formation of endothelial vessels	[255, 256]
	Heparinase	Stimulating macrophages to secrete TNF-alpha	[257]
	miR-34a, miR-125b- 5p, miR-146a, miR-15a, miR – 137/197, miR- 21, miR-17–5p, bFGF	- Stimulate the development of endothelial vessels. - Enhance the growth and advancement of multiple myeloma.	[86, 244, 255, 258]
DLBCL	Wnt3a	Facilitate the proliferation of DLBCL cells	[21]
Lymphoma	LMP1	Enhanced growth and aggressive nature in primary B-cell	[259]
	MICA/B	Declined the NK cell cytotoxicity	[260]
	Doxorubicin, pixantrone	Cells successfully eliminated chemotherapeutic medicines	[261]
	CD20	The bioavailability of rituximab is reduced when combined with it.	[262]
	CK2	Phosphorylation of C9 was carried out in order to protect cancerous cells	[263]
Burkitt	LMP1	Enhanced growth and aggressive nature in primary B-cell	[259]
Leukemia	MICA/B	Declined the NK cell cytotoxicity	[260]
APL	MRP1	The drug-resistant proteins were exchanged among tumor cells through transfer	[234, 264, 265]
ATL	Tax, AKT, Rb, cFLIP, NF-kB	Improved cell viability in murine and human T-cell cultures	[63]

(IL-15), which disrupt the blood-brain barrier (BBB) in engrafted mice, highlighting the role of exosomes in facilitating metastasis. Knocking down IL-15 or interleukin-15 receptor alpha (IL-15Ra) reduces B-cell precursor acute lymphoblastic leukemia (BCP-ALL) cell invasion into the central nervous system (CNS) [27].

Similarly, exosomes derived from chronic myeloid leukemia (CML) cells can be absorbed by endothelial cells, enhancing endothelial cell tube formation, which is a key process in angiogenesis and tumor growth [19]. Research from Tokyo Medical University revealed that *pre-miR-92a* from *K562* exosomes could reduce the expression of the target gene *integrin a5*, while increasing endothelial cell motility and tube formation, further demonstrating the pro-angiogenic role of CML-derived exosomes (Table 1) [28]. Moreover, *miR-210* from CML exosomes has been found to interact with the target gene *Ephrin-A3*, playing a critical role in angiogenesis and regulating VEGF signaling, which are essential processes for tumor survival and expansion [29]. In multiple myeloma, bone marrow mesenchymal stem cells (MSCs) secrete exosomes enriched with oncogenes, cytokines, and adhesion molecules (Table 1) [30–32]. Extracellular vehicles (EVs) carrying the markers CD9 and CD38 are found in greater abundance in multiple myeloma (MM) patients [33]. Fibronectin, a key heparan sulfate-binding ligand in MM-derived exosomes, plays a crucial role in facilitating exosome-cell interactions [34]. Furthermore, exosomes from the MM cell line OPM2 are highly concentrated with *miR-21* and *miR-146a*, which significantly promote MSC proliferation by upregulating these miRNAs during coculture CAR (Table 1) [35].

Chronic lymphocytic leukemia (CLL) exosomes are enriched with miRNAs, such as members of the *miR-150*, *miR-155*, and *miR-29* families, as well as *miR-223*, but have limited amounts of transfer RNAs and short ribosomal RNA. This specific miRNA profile could be used to distinguish CLL exosomes from those of other hematological malignancies [36]. Overall, leukemic exosomes play a significant role in leukemia progression by transferring various molecules that alter the function of other cells. Further research is essential to elucidate the exact mechanisms of action and the potential therapeutic implications of these exosomes, which could lead to novel treatment strategies for hematological malignancies (Table 1) [37].

Different functions of leukemic exosomes

Promoting effects of exosomes on angiogenesis

Angiogenesis, the production of new blood vessels from pre-existing capillaries, is crucial for both healthy and pathological conditions [38]. For malignant tumors larger than 1 to 2 mm, neovascularization is an essential stage in their growth [39]. Exosomes can influence tumor angiogenesis by altering target cells or transferring angiogenic proteins or miRNAs that promote endothelial cell (EC) activity [40]. This section focuses on the role that exosomes play in hematological illnesses, including acute and chronic myeloid leukemia, acute and chronic lymphocytic leukemia, multiple myeloma, and lymphomas, all of which have been linked to increased angiogenesis [40–43]. Patients with advanced myelodysplastic syndromes exhibit higher bone marrow micro vessel density than healthy individuals, indicating that tumor angiogenesis significantly contributes to these conditions [44].

Taverna et al. demonstrated that exosomes released by CML cells directly affect ECs by promoting neovascularization, both in vitro and in vivo [45]. Their research showed that ECs secrete proangiogenic cytokines, such as interleukin-8, when influenced by these exosomes [46]. Additionally, Taverna et al. discovered that *LAMA84* exosomes express *miR-126*, a miRNA involved in angiogenesis, at levels six times higher than those in parental cells. The transfer of *miR-126* from exosomes to ECs impacts the mRNA 3' UTR of *CXCL12* and *VCAM1*, thereby affecting the migratory and adhesive abilities of CML cells [47]. Moreover, CML-derived exosomes induce human umbilical vein endothelial cells (HUVECs) to form tube-like structures resembling blood vessels by transporting *miR-92a* and activating Src signaling (Fig. 1; Table 1) [48].

The role of hypoxia in promoting tumor angiogenesis is well established. Numerous studies have shown that hypoxia increases the production of micro vesicles by human cancer cells, altering the cellular microenvironment and promoting tumor angiogenesis and dissemination [49]. Additionally, microarray and proteomic studies indicate that hypoxic stimuli increase proangiogenic factors in exosomes [50, 51]. Tadokoro et al. reported that *K562* leukemia cells release exosomal miRNAs under hypoxia, promoting tube formation in HUVECs by inhibiting the EPHRIN-A3 ligand. They found that *miR-210* levels are higher in hypoxic exosomes than in normoxic ones, highlighting a key difference [50].

In AML, both in vitro and in the sera of patients, the release of EVs has been documented [50]. Kurre and colleagues demonstrated that AML exosome trafficking influences angiogenic responses in co-cultured stromal and hematopoietic progenitor cell lines, affecting bone marrow invasion [21]. Angiogenesis also plays a significant role in the pathogenesis and progression of multiple myeloma (MM) within the bone marrow [45]. Recent studies have highlighted the interplay between tumors and host environments in MM, driven by exosomes [45]. Liu et al. revealed that myeloma RPMI 8226 cells express micro vesicles (MVs) carrying oncogenic CD138, an angiogenic regulator, which reprogram ECs upon incorporation [45]. Exosome stimulation specifically promotes

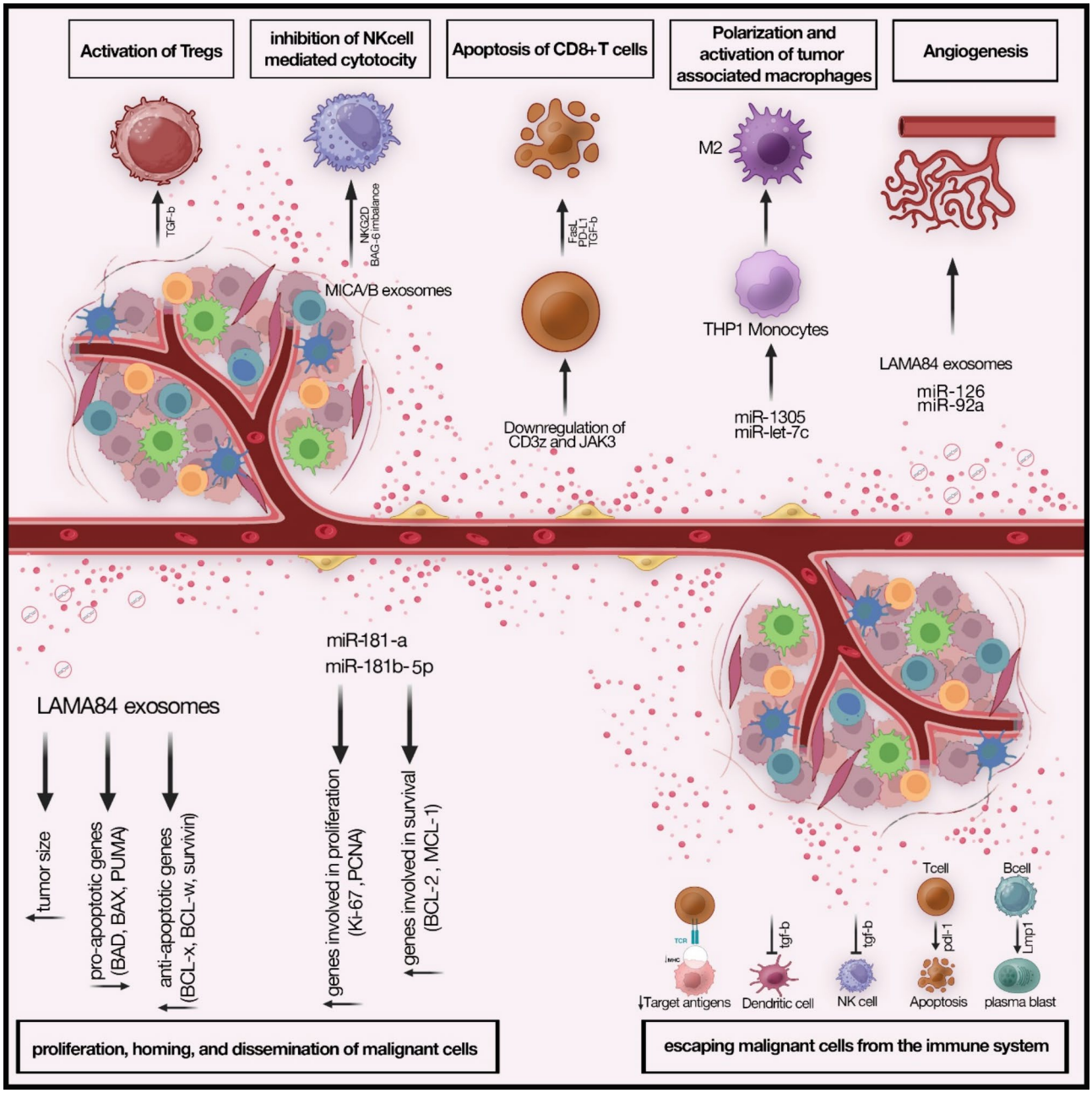

Fig. 1 Tumor cells evade the host immune system by reducing the expression of target antigens, regulating immune responses with tumor-derived miRNAs, and activating regulatory T cells (Tregs) via TGF-β1. Exosomes containing MICA/B act as decoys to bind NK cell receptors like NKG2D, down-regulating their activity and cytotoxicity. Similarly, leukemic exosomes suppress CD3ζ and JAK3 in CD8 + T cells, inducing apoptosis through the Fas/FasL pathway. These mechanisms collectively impair NK and T cell function, allowing tumor cells to escape immune detection. Tumor exosomes can skew immune cell phenotypes to favor tumor progression. For instance, exosomes carrying miR-1305 or miR-let-7c polarize monocytes into tumor-associated macrophages (M2), creating an immunosuppressive microenvironment. CML-derived exosomes modulate the bone marrow niche, promoting tumor-supportive macrophages while regulating inflammatory mediators. Exosomes from AML and CML cells transfer coding and non-coding RNAs that enhance tumor proliferation, survival, and migration. For example, miR-181a and miR-181b-5p upregulate genes involved in cell proliferation and survival, such as PCNA and BCL-2. Angiogenesis is also promoted by exosomes containing pro-angiogenic factors such as miR-126 and miR-92a. These molecules enhance endothelial cell activity and neovascularization, ensuring a supportive blood supply for tumor expansion. [The figures were designed by using biorender shapes (https://www.biorender.com)]

EC proliferation, invasion, and the release of proangiogenic mediators IL-6 and vascular endothelial growth factor (VEGF) [52]. Collectively, these findings underscore the critical role of exosomes in tumor-host communication, which aids in cancer cell growth and spread by modulating angiogenic processes [46].

Suppressive effects of exosomes on Immune responses

In healthy conditions, natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) are crucial for identifying and eliminating cancerous cells. Advances in cellular therapy have led to the development of genetically engineered immune cells, such as CAR-T and CAR-NK cells, which enhance the immune system's ability to attack tumor cells [53–55]. However, tumor cells have developed several strategies to evade the immune system, a phenomenon known as immune evasion [56–58]. One such strategy involves the secretion of exosomes, small extracellular vesicles containing immunosuppressive molecules that directly inhibit NK and CTL cells [59, 60]. For example, exosomes derived from the plasma of patients with acute myeloid leukemia (AML) contain immunosuppressive components such as FasL, PD-L1, and TGF-β [61].

NK cells recognize non-MHC class I ligand molecules through activator receptors on their surface, including natural cytotoxicity receptors (NCRs) and the Natural Killer Group 2 Member D (NKG2D) homodimer. NK cells can destroy target cells when NKG2D binds to its ligand, MHC class I chain-related molecules A/B (MICA/B), expressed on tumor cells [62]. However, exosomes from AML patients have been found to contain high levels of TGF-β1, which downregulates NKG2D expression, thereby limiting NK cell activity [62, 63]. This results in a significant reduction in the number and cytotoxicity of NK cells in the peripheral blood of AML patients [64]. Additionally, tumor cells in T- and B-cell leukemia/lymphoma increase the release of MICA/B-containing exosomes under oxidative stress, which act as decoys to bind NKG2D, preventing it from attaching to its ligand on target cells. This mechanism reduces NK cell-mediated destruction of target cells, facilitating tumor immune evasion (Fig. 1) [65].

NCRs such as Natural Killer cell p46-related protein (NKp46), NKp30, and NKp44 stimulate NK cells' killing activity by transducing activation signals [66]. Recent studies have identified B-cell lymphoma2 (BCL2)-related athanogene-6 (BAG-6) as the ligand for NKp30 [67]. Interestingly, while BAG-6-containing exosomes can activate NK cells and enhance their cytotoxicity, soluble BAG-6 in plasma can inactivate NK cells upon interaction with NKp30. Patients with CLL exhibit lower plasma levels of BAG-6-containing exosomes and higher levels of soluble BAG-6, which inhibits NK cell-mediated tumor cell killing. This imbalance suggests a mechanism for tumor cells' immune escape [68].

CTLs express FasL, the ligand for the death receptor Fas, to kill target cells via the Fas/FasL pathway. However, tumor cells can exploit this pathway by releasing exosomes or other extracellular vesicles containing FasL, leading to the programmed cell death of CTLs. This impairs the immune response against tumor cells [69]. Furthermore, AML-derived exosomes downregulate the expression of CD3ζ and Janus kinase 3 (JAK3) in activated T cells, inducing CD8+T cell death through the Fas/FasL pathway and thereby reducing CD8+T cell functionality [70]. Tumor cell-derived exosomes can also inhibit CD8+T lymphocytes through TGF-β (Fig. 1) [18].

Extensive research has been conducted on the impact of leukemic exosomes on immune cells, highlighting their significant role in the pathophysiology and progression of leukemia [71]. Leukemic exosomes can modify immune cell function in several ways, including inhibiting immune responses, promoting immune cell proliferation, and polarizing immune cells toward an immunosuppressive phenotype. These effects have important implications for developing novel therapeutic strategies for leukemia [72].

One of the key effects of leukemic exosomes on immune cells is the inhibition of immune responses [73]. For instance, exosomes from AML cells have been shown to prevent the activation of T cells and natural killer (NK) cells, thereby impairing immune surveillance and tumor control [70]. Additionally, the bone marrow environment in MM is immunosuppressive due to the presence of cells such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) [74]. MM- and multiple myeloma bone marrow stromal cells (MM-BMSC)-derived exosomes stimulate MDSC growth and activation through pSTAT1 and pSTAT3 signaling pathways, leading to the suppression of T-cell proliferation both in vitro and in vivo [75]. In addition to inhibiting immune responses, leukemic exosomes can promote the proliferation of certain immune cells [71]. For example, exosomes from AML cells encourage the expansion of regulatory T cells, which are essential for maintaining immunological homeostasis and controlling autoimmune reactions [76]. Similarly, exosomes from CLL cells have been shown to induce B cell proliferation, thereby increasing the populations of immune-suppressive cells [77].

Finally, leukemic exosomes can influence the differentiation and polarization of immune cells, leading to the development of immunosuppressive phenotypes [72]. CML-derived exosomes may skew T cells towards tumor-favorable phenotypes rather than conventionally activated T cells [78]. Additionally, MM cells exposed to hypoxia produce more exosomes containing miR-1305,

which, when delivered to THP1 monocytes, induce M2 polarization (Fig. 1) [79]. Multiple Myeloma-derived Mesenchymal Stem Cells (MM-MSC) cells can also promote the polarization of peripheral blood mononuclear cells (PBMC)-derived macrophages into M2 macrophages by transferring *miR-let-7c* [80]. Studies have shown that exosomes produced by K562 CML cells can transform the local bone marrow niche into a leukemia-supportive environment by regulating inflammatory mediators (TNF-α and NO), redox potential, and the polarization of Bone Marrow Mesenchymal Stem Cells (BM-MSCs) and macrophages towards tumor-associated macrophages [81, 82].

Malignant cells escaping from the immune system

One of the characteristics of tumor cells is their ability to evade the host immune system [83]. They achieve this through various mechanisms, including reducing the expression of target antigens, regulating immune evasion with tumor-derived miRNAs, activating regulatory T (Treg) cells, and enhancing suppressive mediators, particularly transforming growth factor β1 (TGF-β1) (Fig. 1) [83, 84]. Leukemic cells produce exosomes that suppress the immune system, facilitating immune evasion [63]. These exosomes contain a variety of proteins related to exosome targeting, the tetraspanin family, lactadherin, Mac-1, apoptosis (FasL, APO2/TRAIL), micro vesicular structure, and antigen presentation (MHC, costimulatory molecules, and heat shock proteins) [85].

An in vitro study on B-cell lymphoma revealed the role of exosomes in disease development. B cells infected with the Epstein-Barr virus (EBV) secrete exosomes containing latent membrane protein 1, which activates CD40 signaling and induces B cell proliferation into plasma blast-like cells [86, 87]. EBV and HIV-1 can cause antigen-presenting cells to overexpress programmed death ligand-1, thereby increasing T lymphocyte apoptosis. In a live mouse model, exosomal miRNAs released by EBV-positive lymphoma cells were transported to macrophages, aiding in the progression of lymphoproliferative disease [88]. Moreover, TGF-β1 levels in tumor-derived exosomes (TDEs) are higher than those in exosomes from normal cells [89]. The production of TGF-β1 by tumors is a major immunological control mechanism that affects NK cell function [90].

NK cells are essential components of the anti-tumor immune response but are dysfunctional in various hematological cancers, including CLL [68]. NKG2D, a key activating receptor on NK, Natural Killer T cells (NKT), and CD8+T cells, is downregulated or inactivated in cancer cells, playing a significant role in immune evasion [64]. In AML patients, exosome-derived TGF-β1 suppresses NKG2D expression, significantly reducing NK cell cytotoxicity [61, 64]. Thus, exosomes in the plasma of AML patients modulate innate immune responses. IL-15 acts as an antagonist by disrupting the SMAD signaling pathway and protecting NK cells [61]. Additionally, AML-derived exosomes induce immunological tolerance in DCs, which is crucial for tumor immune evasion [91]. These TDEs inhibit DC development and activity due to TGF-β1 [92, 93].

These findings demonstrate multiple ways in which exosomes released by leukemia cells support hematological malignancies. They significantly impact cancer progression by influencing immune cells, either enhancing or suppressing their function. Investigating these escape pathways may help prevent the spread of leukemic cells [73].

Proliferation, homing and dissemination of malignant cells

Leukemic exosomes are rich in RNA and protein contents that can favor carcinogenesis. For instance, exosomes from AML contain both coding and non-coding RNAs that contribute to AML progression [94, 95]. These exosomes can transfer their contents to neighboring normal cells and spread throughout the body, thereby promoting the dissemination of malignancy. This phenomenon has been reported in numerous studies. For example, in a xenograft mouse model of CML, exosomes from LAMA84 cells were found to increase tumor size, reduce the expression of pro-apoptotic genes such as *BAD*, *BAX*, and *PUMA*, and increase the expression of anti-apoptotic genes such as *survivin*, *BCL-xl*, and *BCL-w*. These exosomes contain TGF-β1, which promotes tumor cell proliferation, increases tumor size, and modulates gene expression in an autocrine manner (Fig. 1) [96].

Adult T-cell leukemia/lymphoma (ATLL) primarily occurs due to infection with human T-lymphocyte virus type I (HTLV-I). A study showed that cells infected with HTLV-I release exosomes containing the Tax protein, viral mRNA transcripts, and pro-inflammatory mediators, which favor leukemia progression. These exosomes increase cell viability through phosphorylation and activation of AKT and protect cells from apoptosis via the cFLIP-dependent pathway and induction of the NF-kB signaling pathway (Table 1) [97].

In pediatric acute lymphoblastic leukemia (pALL), serum exosomes containing *miR-181a* have been shown to upregulate genes involved in proliferation, such as *PCNA* and *Ki-67*, and survival, such as *MCL-1* and *BCL-2*. Inhibition of *miR-181a* decreased leukemic cell proliferation in vitro, suggesting it as a potential therapeutic target for pALL [98]. Additionally, exosomes containing *miR-181b-5p* play a crucial role in ALL pathogenesis by promoting proliferation, invasion, and migration while inhibiting cell apoptosis (Fig. 1) [99].

Conversely, exosomes derived from MSCs containing *miR-23b-5p* suppress AML cell proliferation,

prevent the transcription of Tripartite Motif Containing 14 (TRIM14), and subsequently inhibit the PI3K-AKT signaling pathway [100]. Moreover, bone marrow MSC-exosomes overexpressing *miR-7-5p* can increase apoptosis and decrease the survival of AML cells by inhibiting the AKT-PI3K-mTOR signaling pathway [101]. Furthermore, BMSC-exosomes containing *miR-222-3p* have been shown to inhibit the proliferation of the THP-1 leukemic cell line and demonstrate pro-apoptotic effects by targeting Interferon Regulatory Factor 2 (IRF2) and negatively regulating the IRF2/INPP4B signaling pathway [102].

Exosome roles in hematological malignancies

Recent research has significantly advanced our understanding of the role exosomes play in the early detection, prognosis, and monitoring of hematological malignancies. This section explores how specific exosomal components, such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), serve as biomarkers for various blood cancers. For instance, exosomal long non-coding RNA *HOTAIR* has been identified as a potent biomarker for the early diagnosis of acute lymphoblastic leukemia (ALL), with elevated levels correlating directly with disease progression [103, 104]. Similarly, exosomal *miR-125b* and *miR-150* have been highlighted as indicators of relapse in acute myeloid leukemia (AML), aiding in the monitoring of treatment responses and disease progression [105, 106].

In the context of multiple myeloma (MM), studies have underscored the importance of exosomal *miR-21* as a predictor of relapse. A 2023 study revealed that patients with elevated exosomal *miR-21* levels face a significantly increased risk of recurrence, presenting a valuable non-invasive biomarker for early detection and disease monitoring [107, 108].

Acute myeloid leukemia

AML is a hematologic neoplasm characterized by significant disruption in cellular differentiation and aberrant proliferation of myeloid progenitor cells [109]. Extensive research has highlighted the potential of using exosomes as a diagnostic tool for leukemia. In recent years, substantial evidence has confirmed the stable presence of long non-coding RNAs (lncRNAs) within exosomes, which holds significant implications for cancer diagnosis, prediction, and surveillance [110].

Recent studies have demonstrated the utility of plasma exosomal lncRNAs—specifically *LINC00265*, *LINC00467*, *UCA1*, and *SNHG1*—as promising cell-free biomarkers for AML diagnosis and treatment monitoring. Notable alterations in the expression levels of these lncRNAs have been observed in the plasma exosomes of AML patients compared to healthy donors (HD). Specifically, *LINC00265*, *LINC00467*, and *UCA1* were downregulated, while *SNHG1* was upregulated in AML patients. These dysregulations suggest that exosomal *LINC00265*, *LINC00467*, *UCA1*, and *SNHG1* can effectively distinguish AML patients from HD. The combined diagnostic efficacy of these lncRNAs underscores their robust potential as a composite panel for identifying AML patients. Consequently, these findings highlight the promise of plasma exosomal lncRNAs as diagnostic biomarkers for AML, warranting further investigation into their diagnostic performance and the clinical relevance of other exosomal non-coding RNAs (ncRNAs) in AML (Table 2) [111].

Additionally, a study found that increased levels of plasma exosome-derived *miR-532* correlated positively with overall survival rates and negatively with energy production indicators, such as glutamine and fructose, in AML patients. However, no significant associations were observed between *miR-532* expression and variables such as white blood cell counts, age, French-American-British (FAB) subtypes, cytogenetic risk groups, or the presence of *FLT3-ITD*, *NPM1*, *CEBPA*, and *DNMT3A* mutations (Table 2) [112].

Another investigation revealed that heightened levels of exosomal *miR-125b* were associated with adverse prognosis in adult AML patients. The concentration of circulating exosomal *miR-125b* served as an independent prognostic indicator for individuals with intermediate-risk AML, correlating with higher risks of disease relapse and overall mortalit (Table 2) [113].

Furthermore, serum exosomes from AML patients exhibited positive immunoreactivity for exosome markers, including TSG101, CD63, Flotillin-1, and CD9. Notably, serum EV-miR-10b levels were markedly elevated in AML patients, especially those with cytogenetically normal AML (CN-AML), compared to healthy controls. A strong correlation was observed between serum EV-miR-10b expression and aggressive clinical characteristics of AML. Receiver operating characteristic analysis demonstrated the diagnostic potential of serum EV-miR-10b, with an area under the curve of 0.875, a specificity of 77.89%, and a sensitivity of 82.50%. Higher serum EV-miR-10b levels were associated with significantly shorter overall survival rates, underscoring its prognostic value as an independent indicator for AML patient outcomes (Table 2) [114].

Hornick et al. identified a distinct group of upregulated serum exosomal miRNAs, including *miR-150*, *miR-155*, and *miR-1246*, highlighting their potential as minimally invasive early biomarkers for AML [115]. Furthermore, the expression levels of *miR-425-5p* were notably decreased in CD34+CD38- AML cells from primary AML patients compared to bone marrow cells from healthy individuals. Similarly, *miR-425-5p* expression was

Table 2 Source, content, application and isolation methods of leukemic exosomes

Type of hematological malignancy	Application	Source of exosomes	Method of exosome/exosomes' RNA isolation	Contents of exosomes	Outcome	Ref.
AML	Diagnostic biomarker and treatment monitoring	Plasma	ExoRNeasy Midi Kit	lncRNAs, namely LINC00265, LINC00467, UCA1, and SNHG1	↓ LINC00265, LINC00467, and UCA1 expression in AML patients ↑ SNHG1 expression in AML patients ↓ LINC00265 and LINC00467 expression associated with younger age ↓ Expression of LINC00467 and UCA1 correlated with increased WBC count ↑ Expression of LINC00265 and LINC00467 at first complete remission (CR) ↑ LINC00265 levels upon the allo-HSCT treatment ↓ SNHG1 levels upon the allo-HSCT treatment	[111]
	Diagnostic and prognostic biomarker	Plasma	ExoRNeasy Midi Kit	miR-532	↑ miR-532 levels positively correlated with overall survival rates ↑ miR-532 levels negatively association with low energy production indicators, such as glutamine and fructose in patients with AML No associations between miR-532 expression levels and WBC counts, age, FAB subtypes, cytogenetic risk groups, and the presence of FLT3-ITD, NPM1, CEBPA, and DNMT3A mutations	[112]
	Prognostic biomarker	Serum	ExoQuick Plasma prep and Exosome Precipitation Kit	miR-125b	↑ Levels of miR-125b in serum exosomes of AML patients ↑ Levels of miR-125b in serum exosomes of relapsed patients compared to non-relapsed patients ↑ Levels of miR-125b serum exosomes in dead patients compared with survived patients ↑ Levels of miR-125b associated with increased risks of relapse and death in patients with FLT3 mutation ↑ Levels of miR-125b related to increased risks of relapse and death in patients with MLL mutation	[113]
	Prognostic biomarker	Serum	Total exosome isolation (TEI) reagent	miR-10b	↑ Expression levels of serum EV-miR-10b in AML patients No significant difference of serum EV-miR-10b expression among different subtypes of AML ↑ Serum EV-miR-10b expression levels in all AML subtypes than normal controls ↓ Serum EV-miR-10b levels in favorable cytogenetic group than those in intermediate or poor cytogenetic group The association between serum EV-miR-10b level and WBC count or blast percent No correlation between serum EV-miR-10b level and hemoglobin level or platelet count Serum EV-miR-10b levels well differentiate AML patients from normal controls ↑ Serum EV-miR-10b associated with aggressive clinical features, including WBC, BM blasts, and cytogenetics No significant relationship between serum EV-miR-10b expression and age, sex, FAB subtype, and WHO classification ↑ OS/DFS in AML patients with low serum EV-miR-10b ↓ Overall survival rates in AML patients with higher serum EV-miR-10b	[114]
	Early biomarker	Serum	ExoQuick™	miR-150, miR-155, and miR-1246	Different levels of exosomal miR-150, miR-155, and miR-1246 in AML patients compared to normal group	[115]

Table 2 (continued)

Type of hematological malignancy	Application	Source of exosomes	Method of exosome/exosomes' RNA isolation	Contents of exosomes	Outcome	Ref.
ALL	Predictive biomarker for CNS infiltration in ALL	Cerebrospinal fluid (CSF)	Ultracentrifugation	miR-181a	Atypical $CD63^{-}/CD81^{-}$ small EVs in high density of CNS^{+} CSF samples of ALL patients	[118]
	Biomarkers for B-ALL	Plasma	Ultracentrifugation	ADAM17 and ATG3	↑ Concentration of exosomes extracted from B-ALL patients than healthy volunteers Different protein profile of B-ALL patient-derived exosomes compared with that of healthy individuals-derived exosomes ↑ Expression of ADAM17 and ATG3 in B-ALL patient-derived exosomes compared with exosomes of healthy controls	[121]
CML	Identification and detection of the BCR-ABL transcript		Size-exclusion chromatography and ExoQuick™	mRNA segment	~ 250-bp band in exosomes derived from CML patients during blast and accelerated phases of CML The ~ 250-bp band with 99% sequence homology with a partial mRNA segment encoding the human BCR-ABL chimeric protein	[122]
MM	Biomarkers	Serum	ExoQuick™	miR-20a-5p, miR-103a-3p, and miR-4505	↓ Levels of serum exosomal let-7c-5p, let-7d-5p, miR-20a-5p, miR-103a-3p, miR-185-5p, and miR-425-5p in MM than in HC group ↑ Levels of serum exosomal miR-4505 and miR-4741 in MM than in HC group No difference in serum exosomal miR-140-3p between the MM and HC groups ↓ Serum exosomal miR-20a-5p, miR-103a-3p, and miR-425-5p levels SMM group than in HC group ↑ Serum exosomal miR-4505 in SMM group than in HC group No difference in the serum exosomal let-7c-5p, let-7d-5p, miR-140-3p, miR-185-5p, or miR-4741 in SMM and HC groups ↓ Levels of serum exosomal let-7c-5p, miR-20a-5p, miR-103a-3p, miR-140-3p, and miR-185-5p in MM group than in SMM group ↑ Levels of miR-4505 and miR-4741 in MM group than in SMM group No difference in serum levels of exosomal let-7d-5p or miR-425-5p between MM and SMM groups	[140]
	Prognostic markers and target for treatment	Bone marrow stromal cells (BMSCs)	Microarray datasets from GEO	miR10a and miR-16	↓ EPHA8 in MM cells caused by exosomal hsa-miR-10a in BMSCs and results in progression of MM ↑ IGF1R and CUL3 exosomal hsa-miR-16 in BMSCs and results in progression of MM	[141]
	Diagnostic marker for monoclonal gammopathies	Serum	miRCURY Exosome Isolation Kit	lncRNA PRINS	Negative correlation between the expression levels of exosomal PRINS and bone marrow plasma cells infiltration in MM patient Negative correlation between the expression levels of exosomal PRINS and albumin levels in MGUS patients Positive correlation between the expression levels of exosomal PRINS and creatinine, lactate dehydrogenase, and β2- microglobulin levels in MGUS patients No dysregulation of PRINS expression levels between patients at different disease stages A correlation between expression levels of PRINS and typical MM chromosomal aberrations, such as gain(1)(q21), del(13)(q14), del(17)(p13), t(4;14), and hyperdiploidy ↓ Exosomal PRINS levels in MM patients was associated with translocation t(4;14) No significant prognostic impact on overall survival for exosomal PRINS No relationship between PRINS expression levels and overall survival	[142]

downregulated in exosomes from AML patients versus healthy individuals. Functional analyses revealed that exosomal *miR-425-5p* from BM-MSCs significantly suppressed AML cell viability, proliferation, invasion, and migration, while inducing apoptosis. *miR-425-5p* inhibited the expression of Wilms tumor 1-associated protein (WTAP), and overexpression of WTAP reversed the inhibitory effects of *miR-425-5p* on AML cell proliferation, apoptosis, migration, and invasion (Table 2) [116].

Moreover, exosomes from AML cells have been shown to suppress the expression of the hematopoietic factor Dickkopf-related protein 1 (DKK1), leading to downregulation of promoters associated with hematopoietic stem cells in bone marrow stromal cells. This creates a supportive microenvironment for leukemia cell proliferation and survival. Additionally, AML-derived exosomes overexpress *miR-21* and *miR-29*, which promote the survival of healthy hematopoietic stem cells while inducing leukemia-like characteristics (Table 2) [117].

Acute lymphoblastic leukemia

Recent research has highlighted the significant role of exosomes in the progression and treatment of ALL. Studies have confirmed that exosomes derived from Precursor B-cell Acute Lymphoblastic Leukemia (pre-B ALL) cells in patients with Philadelphia chromosome-positive (Ph+) ALL can promote the growth of non-growing pre-B ALL cells independently of direct intercellular contact. These exosomes contain miRNAs (exo-miRNAs) that interact with the surrounding microenvironment, facilitating the development of B-ALL cells by stimulating cell proliferation and migration, while also modulating the tumor microenvironment. This interaction ultimately inhibits immune surveillance and anti-tumor responses [118].

Central nervous system (CNS) recurrence in ALL substantially increases the mortality rate among patients. Although research on the involvement of exosomes and miRNAs in CNS metastasis of ALL is scarce, findings by Hua Zhang et al. (2009) indicate that *miR-181a* and specific EV subtypes in cerebrospinal fluid are predictive markers for CNS infiltration in ALL. Significantly, the sensitivity of detecting cerebrospinal fluid *miR-181a* for early diagnosis of CNS leukemia (90%) was substantially higher than that of conventional cytology (54.5%). Additionally, *miR-181a* has been reported to induce B lymphocyte proliferation specifically in pediatric ALL (PALL), with a distinct and substantial amplification of exo-miR-181a observed in PALL sera and leukemia cell lines [119]. Researchers successfully transfected *miR-181a* inhibitors into exosomes, leading to the inhibition of exosome-induced cell proliferation by downregulating pro-survival genes (*MCL-1* and *BCL2*), proliferative genes (*PCNA* and *Ki-67*), and pro-apoptotic genes (*BAD* and *BAX*). Importantly, using exosome transport-targeting miRNA inhibitors offers enhanced safety (Table 2) [118].

Furthermore, another study indicated that EVs derived from patients with ALL can facilitate the progression of ALL cells through the presence of *miRNA-181b-5p*. These EVs influence the cell cycle and inhibit apoptosis in cancer cells, providing a valuable basis for future investigations into the impact of EVs on the development and behavior of ALL [120].

In a recent study, the proteomic composition of exosomes obtained from the plasma of individuals diagnosed with B-ALL was investigated, leading to the identification of 342 differentially expressed proteins (DEPs). The results indicated that the upregulation of ADAM17 and ATG3 within plasma exosomes could potentially play a role in the advancement of B-ALL. Specifically, ADAM17 may contribute to the activation of the Notch signaling pathway, while ATG3 may be involved in the induction of autophagy. These findings hold considerable promise for developing innovative approaches for the diagnosis and treatment of B-ALL (Table 2) [121].

Chronic myeloid leukemia

Extracellular vesicles originating from two distinct humans' CML cell lines were found to exhibit a distinct band measuring approximately 250 base pairs (bp) in size. Subsequent analysis of the RNA sequence within this band revealed a remarkable 99% sequence homology with a partial mRNA segment encoding the human Breakpoint Cluster Region- Abelson Murine Leukemia Viral Oncogene Homolog 1 (*BCR-ABL)* chimeric protein. Notably, this characteristic of ~250-bp band was also observed in exosomes derived from CML patients. However, it was primarily detected in patients during the blast and accelerated phases of the disease. These findings provide compelling evidence that exosomes derived from CML serve as potential targets for the identification and detection of the BCR-ABL transcript; thereby, presenting a promising avenue for novel diagnostic strategies in the context of CML (Table 2) [122].

A study aimed at investigating the impact of exosomes in chronic myeloid leukemia has revealed compelling evidence regarding their functional role. Specifically, exosomes derived from the K562 cell line, representing the erythroleukemia subtype, were found to elicit the phosphorylation of Src, a target sensitive to dasatinib, as well as activate downstream proteins in endothelial cells [123]. Furthermore, another investigation demonstrated that *miR-92a*, originating from K562 exosomes, exhibited the ability to downregulate the expression of *integrin a5*, consequently enhancing endothelial cell mobility and the formation of tubular structures (48). Additionally, *miR-210*, present in CML exosomes, was shown to interact

with *Ephrin-A3*, a target gene involved in angiogenesis and the signaling pathway mediated by VEGF. Collectively, these findings shed light on the intricate involvement of exosomal miRNAs in angiogenesis and VEGF signaling, presenting novel insights into the mechanisms underlying CML progression (Table 2) [50].

Lymphomas

Malignant lymphomas, encompassing Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), constitute a varied array of disorders originating from the clonal proliferation of lymphocytes. With over 30 distinct types, each lymphoma presents a unique natural course. This biological diversity leads to significant variations in epidemiology, pathological features, clinical manifestations, and preferred treatment strategies among lymphomas [124].

Studies have shown elevated levels of EVs containing *miR-24-3p*, *miR-127-3p*, *miR-21-5p*, *miR-155-5p*, and *Let-7a-5p* in the plasma of Hodgkin lymphoma patients compared to control individuals [125]. Examination of plasma EV miRNA profiles in classical HL patients prior to treatment revealed elevated concentrations of these miRNAs. Notably, post-treatment levels of these miRNAs declined with complete metabolic response, only to rise again in patients experiencing relapse (Table 2) [126].

Exosomes and their cargo present potential as non-invasive biomarkers for monitoring diffuse large B-cell lymphoma (DLBCL) patients' post-treatment. Research identified a set of five miRNAs (*hsa-miR-379-5p*, *hsa-miR-135a-3p*, *hsa-miR-4476*, *hsa-miR-483-3p*, and *hsa-miR-451a*) as biomarkers derived from exosomes in DLBCL. Some miRNAs (*hsa-miR-379-5p*, *hsa-miR-135a-3p*, and *hsa-miR-4476*) exhibited higher expression levels in DLBCL compared to healthy individuals, while others (*hsa-miR-483-3p* and *hsa-miR-451a*) showed reduced expression [127]. Additionally, exosomal *miR-15a-3p*, *miR-21-5p*, and *miR-181a-5p* have emerged as promising miRNA candidates for the distinct diagnosis of DLBCL [128].

Further investigations have uncovered anomalous levels of three forms of exosomal *miR-181-5p*, specifically suggesting a reduction in expression across *miR-181a-5p*, *miR-181b-5p*, and *miR-181d-5p*. Consequently, further exploration is necessary to determine if any particular form of exosomal *miR-181-5p* undergoes downregulation in DLBCL [129].

In terms of prognostic relevance, exosomal miRs such as *miR-125b-5p* and *miR-99a-5p* have been linked to shorter progression-free survival (PFS), whereas reduced expression of exosomal *miRNA-107* and *miR-451a* suggests an unfavorable prognosis in DLBCL [129]. A specific study involving 20 DLBCL patients highlighted the prognostic importance of *miR-125b-5p* [130]. Additionally, the combination of *miR-99a-5p* and *miR-125b-5p* has been identified as both biomarkers for DLBCL and predictors of prognosis and treatment outcomes. These miRNAs are commonly found in plasma exosomes and elevated in B-lymphocytes, regulating cell growth and programmed cell death depending on the specific cell type [131]. Notably, *miR-125b-5p* targets *BCL-2*, *LIN28B*, and *p53*, while *miR-99a-5p* can target *SMARCA5*, *SMARC1*, *mTOR*, *IGF-1R*, and *FGFR3*, which are associated with various cellular functions [132].

Distinct miRNA profiles derived from exosomes of both DLBCL parental cells and cells resistant to R-CHOP treatment have been identified. Among these, *miR-99a-5p* and *miR-125b-5p* stand out as potential biomarkers in DLBCL patients, offering predictive value for prognosis and response to chemotherapy. Targeting these miRNAs may present novel therapeutic avenues. However, further exploration through large-scale multicenter retrospective and/or prospective studies is essential to validate these findings comprehensively [133].

The presence of exosomal *miR-451a* has demonstrated prognostic significance. Combining *miR-451a* with the International Prognostic Index (IPI) may offer an improved means of predicting both progression-free survival (PFS) and overall survival (OS) among DLBCL patients [134]. Other studies identified *miR-155* as a valuable biomarker in individuals with monoclonal B-cell lymphocytosis and those diagnosed with B chronic lymphocytic leukemia. Elevated levels of exosomal *miR-155* were found in refractory/relapsed DLBCL patients compared to those responding to treatment or still undergoing R-CHOP therapy [135, 136].

A comprehensive study examining the entire plasma mirnome, including its exosomal component, in DLBCL patients revealed notable alterations. Specifically, increased plasma levels of *miR-124* and *miR-532-5p* were observed, alongside decreased levels of *miR-425*, *miR-141*, *miR-145*, *miR-197*, *miR-345*, *miR-424*, *miR-128*, and *miR-122*. Elevated levels of *miR-20a*, *miR-20b*, *miR-93*, *miR-106a*, and *miR-106b* were associated with increased mortality [137].

In DLBCL patients, a notable increase in plasma exosome levels was identified, accompanied by a significant decrease in the expression of 33 miRNAs within these exosomes. Normal B-cells internalize exosomes derived from DLBCL, leading to specific miRNA expression differences in these cells, unique to different subtypes of lymphoma. The findings suggest that *miR-3960*, *miR-6089*, and *miR-939-5p* could serve as a signature for DLBCL diagnosis. It is hypothesized that exosomes alter the molecular signature of target cells based on the genomic characteristics of the lymphoma cells from which they originate [138].

Multiple myeloma

Serum-derived exosomal miRNAs have emerged as promising biomarkers for MM and are thought to play a significant role in the progression of monoclonal gammopathies. These miRNAs, encapsulated within serum exosomes, hold potential for diagnostic and prognostic applications in MM and may provide valuable insights into the underlying mechanisms involved in the development and advancement of monoclonal gammopathies [139].

In one study, significant variations were observed in the levels of serum exosome-derived *miRNA-20a-5p*, *miRNA-103a-3p*, and *miRNA-4505* among individuals diagnosed with MM, those with smoldering multiple myeloma (SMM), and control subjects. This finding highlights the potential utility of these specific miRNAs as markers for distinguishing MM and SMM patients from healthy individuals (Table 2) [140].

Another investigation reported that differentially expressed miRNAs (DEMs) originating from bone marrow MSCs could discriminate between individuals with MM, normal controls, and those with MM-monoclonal gammopathy of undetermined significance (MGUS) in the GSE39571 dataset. Additionally, one downregulated DEM and one upregulated DEM (specifically *hsa-miRNA-10a*) could distinguish MM from normal controls and MM-MGUS controls in the merged dataset combining GSE110271 and GSE78865. When comparing MM samples with normal samples, 11 downregulated DEMs (including *hsa-miRNA-16*) and one upregulated DEM were found to be shared between the GSE39571 dataset and the merged dataset. The predicted downstream genes targeted by these 17 DEMs revealed that *IGF1R* and *CCND1* were particularly relevant genes regulated by *hsa-miRNA-16*. Exosomal miRNAs *hsa-miRNA-10a* and *hsa-miRNA-16*, originating from BMSCs, may play a role in the progression of MM by controlling the expression of genes such as *EPHA8*, *IGF1R*, *CCND1*, *CUL3*, and *ELAVL1*. These exosomal miRNAs have the potential to serve as prognostic markers for disease progression and may represent viable targets for novel therapeutic approaches [141].

Additionally, another investigation revealed a modification in the exosomal long lncRNA *PRINS* between individuals with MM and healthy controls. Specifically, MM and MGUS subjects were distinguished from controls with a specificity of 83.3% and a sensitivity of 84.9%. The concentrations of *PRINS* were associated with characteristic chromosomal alterations in MM, including del(13)(q14), del(17)(p13), t(4;14), gain(1)(q21),, and hyperdiploidy. This study suggests that exosomal lncRNA *PRINS* may serve as a potential diagnostic marker for monoclonal gammopathies (Table 2) [142].

The various aspects of exosome-based treatment in hematological treatment

Role of exosomes in leukemia treatment

Dendritic Cells (DCs) pulsed with Tumor-Derived Exosomes (TDE) and exosomes extracted from malignant cells have been employed to elicit an immune response against tumors [143]. Studies have shown that communication among DCs occurs via miRNAs within exosomes and that the composition of exosomes can change as the parental DCs mature [144]. While DCs have a moderate ability to stimulate the immune system, this may not be enough to activate NK cells and T cells adequately. Furthermore, using DCs in therapy could accidentally activate the immunosuppressive actions of Tregs and MDSCs, leading to undesired immune responses [145].

Allogeneic stem cell transplants (SCT) are highly effective in eliminating leukemia and result in marked improvements for individuals with acute myeloid leukemia [146]. Consequently, using T adoptive immunotherapy with alloreactive NK cells holds promise for managing AML patients. When NK cells are activated, they generate abundant exosomes that are absorbed by K562 cells, exhibiting anti-leukemia activity against AML cells, which is influenced by the dose of exosomes [147]. *PTEN*, a tumor suppressor, acts as an inhibitor within the PI3K-AKT pathway. Reports suggest that *miR-21* promotes invasion and proliferation by targeting *PTEN* [148]. The immunosuppressive impact of TDEs is likely attributed to miRNAs, which can also serve as indicators for monitoring patients during treatment. For instance, detecting *miRNA-150*, *miRNA-155*, and *miRNA-1246* in EVs from AML has been suggested for this purpose (Fig. 2; Table 3) [115].

MiR-181a is implicated in the involvement of the CNS in pALL. Inhibiting *miR-181a* holds promise for positive outcomes in PALL treatment [149]. Additionally, *miR-34a* demonstrates significant effectiveness in treating AML patients by suppressing the release of exosomes and promoting cell death through the Janus Kinase 1/Signal Transducer and Activator of Transcription protein-2 (JAK1/STAT2)/p53 pathway [150]. Recent studies have identified exosomal miRNAs, such as *miR-125b* and *miR-146a*, as key modulators in AML pathogenesis and prognosis. Elevated levels of these miRNAs in exosomes are associated with poor outcomes, including increased risk of relapse and resistance to chemotherapy, thus providing potential biomarkers for AML patient monitoring [151]. Moreover, *miR-146a-loaded* exosomes have been shown to enhance the proliferation of bone marrow-derived mesenchymal stem cells (BMSCs), which contribute to AML progression and drug resistance [152]. Exosomal *miR-222-3p*, derived from bone marrow MSCs, triggers apoptosis through the interferon regulatory factor 2 signaling pathway and hampers cell proliferation, presenting

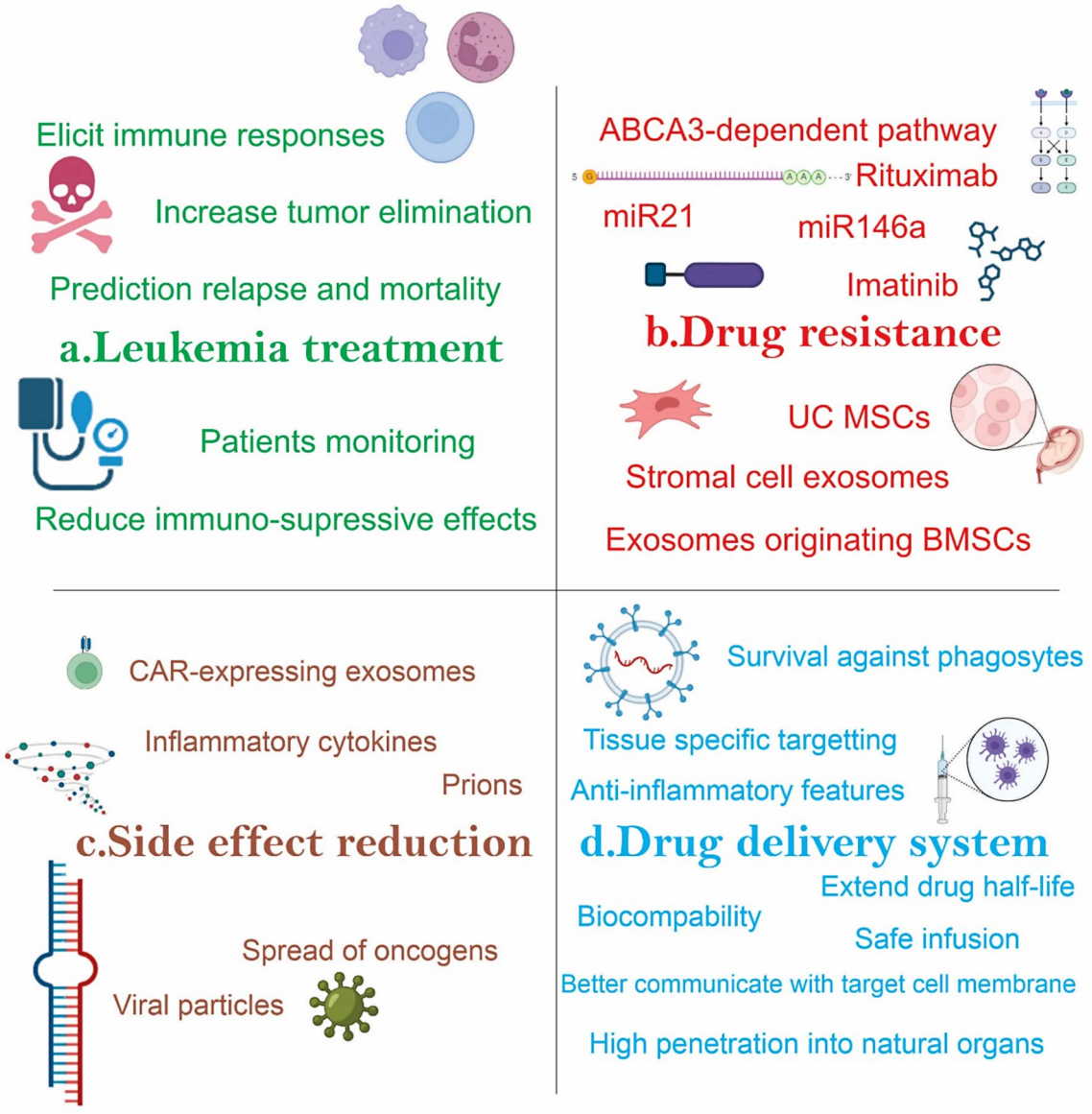

Fig. 2 This figure illustrates the multifaceted roles of exosomes in leukemia treatment, drug resistance, side effect reduction, and drug delivery systems. Leukemia Treatment (**a**): Exosomes can enhance immune responses, increase tumor elimination, and reduce immunosuppressive effects. They also aid in patient monitoring and help predict relapse and mortality rates. Drug Resistance (**b**): Exosomes contribute to drug resistance mechanisms through pathways such as ABCA3 and molecules like miR-21 and miR-146a. Exosomes derived from stromal cells, including those from bone marrow and umbilical cord MSCs, influence resistance to treatments like Rituximab and Imatinib. Side Effect Reduction (**c**): CAR-expressing exosomes and their interaction with inflammatory cytokines and prions reduce side effects, including the spread of oncogenes and viral particles. Drug Delivery System (**d**): Exosomes offer advantages for drug delivery, such as tissue-specific targeting, biocompatibility, anti-inflammatory properties, prolonged drug half-life, and enhanced penetration into natural organs. These features improve safe infusion and interaction with target cell membranes while enabling survival against phagocytosis. [The figures were designed by using biorender shapes (https://www.biorender.com)]

a potential new therapeutic method for myeloid leukemia treatment [102]. Intriguingly, increased expression of *miRNA-125b* within serum exosomes of AML patients is strongly linked to a heightened risk of relapse and mortality, suggesting *miR-125b* as a significant biomarker for forecasting disease remission rates and the probability of relapse (Table 3) [113].

Efforts to employ DCs in vaccinating leukemia patients have shown promising outcomes [153]. For example, a study on personalized DC-based vaccination for CLL revealed a notable reduction in the count of leukemic cells and Tregs in the bloodstream [154]. Similar investigations on different hematological malignancies exhibited comparable outcomes. Exosomes derived from DCs significantly influence the modulation of T cell responses.

Table 3 Exosome-mediated treatment approaches for the treatment of hematological cancers

Cancer Type	Target Cell	Exosomes	Function	Ref.
AML	AML (THP-1)	ND BM-MSC	- ND BM-MSC-exo-miR-222-3p inhibits cell proliferation and promotes apoptosis in THP-1 cells - The mechanism involves targeting IRF2 and negatively regulating IRF2/INPP4B signaling	[102]
	AML (MOLM-14)	AML BM-MSC	Varied defense mechanisms against kinase pathway blockade	[266]
	AML (KG1a, NB4, and MV411)	AML BM-MSC HS5	In a co-culturing system of bone marrow stromal cells (BMSC) and acute myeloid leukemia (AML), the inhibition of exosomes has been found to have a significant impact	[267]
	HS-5 BMSCs	Blocking exosomes	Induced apoptosis	
	NK cells	Exosomes from stimulated NK cells contain key cytotoxic chemicals such as IFN-g, lymphocyte function-associated antigen (LFA-1), DNAX accessory molecule-1 (DNAM1), and programmed cell death protein (PD-1), Increase the immunological response to AML	Enhances the immunological responses	[268]
	U937 cells	PEGylated liposomal doxorubicin (PLD)/GW4896, make U937 cells more susceptible to the cytotoxic effects of PLD	Enhance the sensitivity of U937 cells to the cytotoxic properties of PLD	[240]
	NB4 cell line	BM-MSC-exo treatment	A decrease in S100A4 levels resulted in a suppression of both the proliferation and migration of leukemia cells.	[269]
ALL	ALL pre-B	OP9 ND BM-MSC	The activation of the NF-κB pathway, coupled with the self-induction of Galectin-3 mRNA and MSC-exo-Galectin-3, serves as a defense mechanism for ALL cells against the detrimental effects of nilotinib and vincristine	[270]
	-	exosome-derived miRNA-181a	The suppression of ExomiR-181a led to a decrease in the levels of genes associated with cell growth, including BCL2, PCNA, MCL-1, and KI-67. Additionally, the inhibition of pro-apoptotic genes such as BAX or BAD can restrict the exosome-induced cell proliferation	[271]
	CD19-positive B-cell neoplasms	Chimeric antigen receptor-exosome Cd19	- Increased Cell Toxicity - Programmed cell death	[272]
	LEX cell lines	Exosomes derived from leukemia (LEXTGF-1si)	- Inhibits the growth of leukemia cells - Improves survival rates in animal studies	[273]
CML	CML (K562)	ND UC-MSC	Increased Sensitivity of K562 Cells to IM through Caspase Signaling	[274]
	CML blasts	Imatinib-armed IL3-exosomes	Leukemia cell growth can be suppressed	[275]
	CML cell line	Venetoclax-armed immunoliposome (IL-VX)	Induced Apoptosis	[276]
	CML xenograft in SCID mice	exosomal elimination of miR-21 in curcumin plasma	Contributes to the Anti-cancer Properties of Curcumin	[277]
	CML cells	BM MSC-Exo	MiRNA-15a suppresses the proliferation and apoptosis of tumor cells	[278]
	K562 951 cells	Mesenchymal stromal cell exosomes (hUC-MSC-Exo)	The inhibition of induced cellular viability and programmed cell death	[171]

Table 3 (continued)

Cancer Type	Target Cell	Exosomes	Function	Ref.
Lymphoma	CD11b+/ Gr–1 + cells	Curcumin is contained within exosomes derived from lymphoma cells	- Boosts programmed cell apoptosis - Anti-inflammatory properties	[279]
	L820 lymphoma cells	Exosome-like nanoparticles carrying siRNA	- Suppressing c-Myc in L820 Lymphoma Cells - triggers the activation of polymerase-dependent apoptotic systems.	[280]
	CD21 on B-cell	Gp350c exosomes	The expansion of tumor-associated and EBV-specific T cells has become increasingly prevalent	[281]
MM	MM (MM1S and U266)	MM BM-MSC	Resistance from MM BM-MSCs is transferred to MM cells through the transmission of PIs	[282]
	MM (MM1S and RPMI8226)	Murine BM-MSC, MM BM-MSC, ND BM-MSC	- MM BM-MSC-exo promotes tumor growth - ND BM-MSC-exo inhibits cell growth	[283]
	MM (U266 and OPM-2)	MM BM-MSC ND BM-MSC	- Enhances the proliferation of MM cells - Alleviated the inhibitory impact of miR-15a/miR-16 on BCL-2	[284]
	MM cells (BF01)	Exosomes were produced by cells that had been exposed to antibodies	- Alterations in NK cell gene expression - Decrease in cell cycle-related genes - Increased immune response-stimulating genes	[285]
	HSP70-modified exosomes derived from MM cells	Dcs	- Activation of the Anti-MM Immune Response - Effective CD4+/Th1, CD8+/CTL, NK responses	[286]
	Exosomal circrna	H9C2 cells	A novel Diagnostic Marker for Myocardial Injury	[287]
	MM (5733MMvt and RPMI8226)	Murine BM-MSC MM, BM-MSC ND BM-MSC	- Stimulated c-Jun N-terminal Kinase, p38, p53, and Akt - Enhanced the proliferation of myeloma cells - Developed resistance to bortezomib treatment.	[246]

The transfer of tumor antigens from TDEs to DCs can trigger cytotoxic T lymphocyte responses [155, 156]. Research involving the K562 cell line has shown that DCs can internalize exosomes derived from leukemic cells, leading to the activation of CTLs in vitro and triggering an anti-leukemic response in vivo [157]. However, recent findings indicate that the uptake of AML-derived exosomes by DCs leads to a reduction in the cytotoxic activity of DCs and a decrease in the lysis of K562 cells. Consequently, utilizing a vaccination approach based on exosomes derived from individual patients may not be viable for treating AML patients [91]. Additionally, recent findings highlight the role of exosomes in facilitating immune evasion in leukemia by carrying immunosuppressive molecules such as TGF-β and PD-L1. Targeting these exosomal pathways could enhance the efficacy of leukemia immunotherapies, particularly in patients receiving allogeneic Stem Cell Transplantation (SCT) or NK cell-based therapies (Fig. 2) [158].

Analysis of exosomes in CLL patients revealed that exosome release is regulated through B-cell receptor (BCR) signaling. Specifically, BCR signaling enhances exosome secretion in CLL patients when stimulated by α-IgM. Additionally, ibrutinib, a specific inhibitor of Bruton's tyrosine kinase, effectively hinders BCR signaling [36]. Exosomal TGF-β1 from TDEs can induce immunosuppressive effects. To optimize a vaccination strategy utilizing TDEs, it is essential to counteract the immunosuppressive influence of TDE-derived TGF-β1 [89]. This represents an innovative approach to tumor vaccination using exosomes and can also be beneficial for eradicating minimal residual diseases (MRDs) [159]. The efficiency of exosome uptake varies based on the cell origin when considering target cells. Specifically, NK cells demonstrate a higher uptake rate of exosomes derived from the myeloid system, such as K562 and Jurkat ALL cell lines, compared to exosomes derived from other cell lines like HepG2 (human liver cancer cell line) and MCF-7 (breast cancer cell line) (Table 3) [160].

Research conducted on melanoma cells revealed that exosomes from tumors, acting as drug-delivery vehicles under acidic conditions, facilitated the uptake of drugs by tumor cells. The low pH of the tumor microenvironment (TME) further enabled them to counteract the intrinsic resistance of tumor cells, allowing the accumulation of cytotoxic drugs [161]. A study showed that treatment with curcumin leads to a dose-dependent increase in *PTEN* levels and a reduction in AKT phosphorylation and VEGF expression [162]. Additionally, there is a decrease in *miR-21* levels within chronic myeloid leukemia cells and an increase in *miR-21* levels in exosomes following curcumin therapy [163]. An experiment

conducted on a mouse model demonstrated that mice treated with curcumin had smaller tumors compared to untreated mice (Table 3) [164].

Effects of exosomes on drug resistance

Recent insights into drug resistance highlight the role of exosomes in expelling drugs from cells. Mesenchymal Stem Cells (MSCs) are known to create a microenvironment that favors tumor cells, potentially advancing tumor progression [165]. The interaction between bone marrow-derived mesenchymal stem cells (BMSCs) and leukemic cells significantly contributes to drug resistance. Exosomes originating from BMSCs contain various cytokines and chemokines that enhance the movement, growth, and viability of multiple myeloma cells by preventing the degradation of cleaved caspase-9 and caspase-3. These findings suggest that, despite the distinct compositions of BMSC and malignant cell exosomes, they can communicate effectively (Fig. 2) [166].

Moreover, in B-ALL, the presence of *Gal-3* mRNA and protein in exosomes from stromal cells is linked to drug resistance through activation of the MEK/ERK pathway [167]. An investigation involving OPM2-exo (exosomes derived from multiple myeloma cells) revealed that *miR-21* and *miR-146a* encourage the proliferation of MSCs [35]. Nonetheless, the critical role of exosomes in intercellular communication cannot be underestimated. Conversely, several studies have shown that MSCs inhibit tumor growth [168–170]. A study focusing on K562 cell lines demonstrated that combining exosomes from human umbilical cord MSCs with imatinib led to increased cleavage of caspase-3 and caspase-9 proteins compared to using imatinib alone (Table 3) [171].

Detailed investigations have revealed that exosomal miRNAs such as *miR-21* and *miR-222* are heavily involved in the modulation of drug resistance mechanisms in leukemia. These miRNAs target the PTEN/PI3K/AKT signaling pathway, which plays a key role in cell proliferation and survival [172]. In particular, miR-21-loaded exosomes from BMSCs were shown to suppress apoptosis in leukemia cells by preventing the degradation of pro-apoptotic proteins such as cleaved caspase-3 and caspase-9. Moreover, exosomes from drug-resistant leukemia cells were found to transfer their resistance phenotype to sensitive cells by delivering these miRNAs, exacerbating chemoresistance [173]. To counteract this, engineered exosomes loaded with miRNA inhibitors have shown promise in reversing resistance by targeting these miRNAs and restoring drug sensitivity [174].

Furthermore, the mutual interaction between stromal cells and leukemic cells in living organisms is a primary cause of chemoresistance in acute T cell lymphoblastic leukemia or lymphoma. Therefore, targeting stromal cells could be a promising approach for treating T cell lymphoblastic leukemia [175]. Rituximab, an anti-CD20 chimeric antibody, has long been a conventional immunotherapy for treating malignant B cell lymphoma [176]. However, exosomes originating from lymphoma cells can hinder the effectiveness of rituximab and may even provoke resistance. This resistance is attributed to the presence of CD20 on exosomes derived from B-cell lymphoma cells, which interact with anti-CD20 antibodies and impede the impact of rituximab. Additionally, exosomes released by B cell lymphoma reduce the cytotoxic effects of rituximab. These findings suggest a new drug resistance mechanism in lymphoma involving an ABCA3-dependent pathway for exosome release [177, 178]. Following treatment, an observed rise in exosomal *miR-451a* levels in the serum of DLBCL patients served as an indicator of the effectiveness of rituximab treatment (Fig. 2; Table 1) [179].

The effect of exosomes in the reduction of side effects

Current cancer treatments, although often effective, are limited by their severe side effects, necessitating the development of innovative therapeutic approaches. One promising alternative is CAR-expressing exosomes, which have emerged as targeted tools for cancer treatment with minimal adverse effects [180]. The inherent biological properties of EVs have positioned them as crucial components in drug delivery systems, recognized for their minimal side effects [181].

Dommelen and colleagues proposed that a proteomic analysis of EVs could help prevent undesirable side effects, such as the spread of oncogenes, prions, inflammatory cytokines, or viral particles [182]. Moreover, the use of DC-derived exosomes in treating metastatic melanoma has demonstrated promising results, with only minor side effects such as inflammation and fever. This suggests that exosomes, as drug delivery vehicles, could revolutionize tumor treatment by combining high efficacy with minimal adverse reactions (Fig. 2) [183].

Recent research underscores the potential of exosome-based drug delivery systems to reduce chemotherapy side effects by enhancing drug specificity and reducing systemic toxicity. For instance, exosomes loaded with doxorubicin have demonstrated improved targeting of leukemia cells while avoiding cardiotoxicity, a common side effect associated with doxorubicin use [174]. This has been attributed to the natural membrane composition of exosomes, which enables more efficient and specific uptake by cancer cells compared to free drugs [184]. Additionally, studies have shown that exosomes can be engineered to avoid immune recognition, further reducing the likelihood of inflammatory responses and enhancing the overall tolerability of treatments in patients with leukemia and other hematological malignancies [172].

A recent study has underscored the significant role of cell surface vesicles, a unique category distinct from traditional extracellular vesicles. These vesicles, derived from the cell membrane, effectively reduced drug side effects, particularly those associated with doxorubicin, when compared to control groups [185].

Exosomes as drug delivery system

Exosomes, as natural transporters of molecules, offer significant potential in drug delivery systems (DDS) due to their unique features. These features include the ability to pass biological barriers, safe infusion without inducing graft-versus-host disease (GVHD), survival against phagocytes, natural origin, and anti-inflammatory and pro-regenerative properties [186, 187]. Drugs can be loaded into exosomes or exosome-mimetics either directly or through parental cell engineering [188]. Direct loading methods encompass various techniques such as incubation, electroporation, sonication, artificial exosome fabrication, freeze-thawing, saponin-assisted loading, and hypotonic dialysis. These methods involve loading isolated exosomes with therapeutic cargos such as small molecular weight drugs, nanomaterials, or proteins, offering a simpler approach compared to parental cell engineering. For instance, RNA-based drugs directly engineered into exosomes have shown success in treating Alzheimer's disease (Fig. 2) [189].

Exosome-based drug delivery systems have gained significant attention due to their ability to deliver RNA-based therapeutics, including small interfering RNAs (siRNAs) and microRNAs, directly to target cells [184]. Recent studies have highlighted the success of exosome-loaded RNAi therapies in AML, where KrasG12D-targeting RNAi was successfully delivered via exosomes, leading to a marked reduction in tumor burden in mouse models [152]. Furthermore, exosome-loaded chemotherapeutic agents such as gemcitabine and paclitaxel have been shown to outperform free drug formulations, demonstrating enhanced tumor penetration and decreased systemic toxicity. Engineered exosomes are now being explored in clinical trials as vehicles for the precision delivery of drugs and RNA therapeutics to specific cancer cells, further highlighting their potential in overcoming traditional drug delivery challenges in hematological cancers [173].

In one study, exosomes derived from human foreskin fibroblast cells were engineered to carry RNAi against the KrasG12D mutation in pancreatic cancer, showing improved anti-cancer effects in a mouse model [187]. Similarly, anti-tLyp-1 exosomes loaded with shRNA demonstrated gene knockdown and reduced stemness of cancer cells [190]. Gemcitabine-loaded autologous exosomes exhibited better loading efficiency and promising results in pancreatic cancer [191], while doxorubicin-loaded exosomes showed therapeutic efficacy without cardiac toxicity and better cellular uptake in osteosarcoma cells compared to doxorubicin alone [192].

The parental cell engineering method involves loading drugs or nucleic acids into cells to increase their concentration in the cytoplasm before exosome biogenesis, resulting in their incorporation into the exosomes. For example, MSCs incubated with high doses of paclitaxel secrete exosomes containing paclitaxel, which showed promising anti-proliferative effects on pancreatic adenocarcinoma cells compared to paclitaxel alone [193]. Similar results were achieved with curcumin-loaded exosomes [194]. Exosomes containing oligonucleotides derived from parental cells have shown great outcomes in nucleic acid delivery; for example, HEK293T cells transfected with siRNA targeting c-Met decreased tumor growth and reversed cisplatin resistance in gastric cancer cells in vitro [195]. Transfecting parental cells with various mRNAs, miRNAs, shRNAs, and proteins can create novel exosomes for DDS. For instance, miR-134 exosomes decreased tumor cell invasion and enhanced sensitivity to anti-Hsp90 treatment [196]. Additionally, exosomes can be used in conjunction with oncolytic viruses (OVs). OVs have demonstrated promising results in cancer elimination, and when combined with exosomes, they can enhance therapeutic outcomes. Studies have shown that this combination provides tumor-selective delivery and stimulates a robust immune response at tumor sites (Fig. 2) [197, 198].

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Recent advancements include the use of surface-modified exosomes, conjugated with targeting ligands such as aptamers and antibodies, which have improved targeting specificity and therapeutic efficacy [32, 199]. Moreover, CRISPR-Cas9-loaded exosomes are gaining attention as a groundbreaking approach for gene therapy in hematological malignancies. Studies from 2023 have shown

successful delivery of gene-editing tools directly to leukemic stem cells, enabling precise genetic modifications with minimal off-target effects [32, 200, 201]. Additionally, techniques such as sonication and freeze-thaw cycles have enhanced the loading efficiency of chemotherapeutics like doxorubicin and paclitaxel into exosomes [201].

Critical challenges in achieving targeted delivery and potential solutions

While exosome-based DDS offer immense promise, several challenges must be addressed to fully realize their potential. These challenges have been included in following subheadings.

Heterogeneity in Exosome Composition and Yield

Exosomes are naturally heterogeneous in their composition, which poses challenges in producing consistent, well-characterized exosomes for therapeutic use. The variability in their molecular cargo can lead to inconsistent therapeutic outcomes. Moreover, the yield of exosomes from source cells can be relatively low, which hampers their scalability for clinical applications. As a potential solution, researchers are refining isolation techniques, such as ultracentrifugation, size-exclusion chromatography, and immunoaffinity capture methods, to improve exosome purity and yield. Advances in bioreactor technologies could enable large-scale exosome production. Additionally, genetic engineering of source cells to produce exosomes with a more defined and uniform molecular composition is another promising approach [172].

Targeting efficiency

A major limitation of exosome-based DDS is the difficulty in achieving highly selective targeting to specific tissues or cancer cells. Without adequate targeting, exosomes may be cleared from circulation by the liver or spleen, reducing their therapeutic efficacy.

Engineering exosomes with specific targeting ligands, such as peptides, antibodies, or aptamers on their surface, has shown promise in improving targeting efficiency. For example, modifying the surface of exosomes with ligands that bind to cancer cell-specific receptors, such as folate receptors or integrins, can improve their uptake by target cells. Hybrid exosomes, which combine synthetic nanoparticles with natural exosomes, offer enhanced stability and targeting properties [152].

Immune clearance and recognition

Despite their natural origin, exosomes can still be recognized and cleared by the immune system, particularly by macrophages and the reticuloendothelial system. This immune recognition limits the circulation time of exosome-based therapeutics, reducing their effectiveness. To address this issue, researchers are developing "stealthy" exosomes by engineering their surface proteins or lipids to evade immune recognition. One approach is modifying exosome surfaces with CD47, a protein known to signal immune cells not to phagocytose the exosome. Cloaking exosomes with polymers like polyethylene glycol (PEG) has also been shown to enhance their circulation time and reduce immune clearance [173].

Loading efficiency

Various methods exist for loading therapeutic cargo into exosomes, but the efficiency and stability of this loading can vary. Some drugs may leak out during exosome transport, reducing the overall therapeutic payload delivered to target cells. Recent advancements in electroporation and sonication techniques have shown improved loading efficiency for small molecules and RNA-based drugs into exosomes. Using fusogenic liposomes to deliver cargo into exosomes has also emerged as a promising strategy for enhancing drug loading and retention within exosomes [184].

Regulatory and safety concerns

As with any novel therapeutic, there are concerns regarding the long-term safety and regulatory approval of exosome-based therapies. Issues such as potential off-target effects, toxicity, and the risk of exosomes promoting unintended biological changes must be thoroughly addressed in clinical trials. Rigorous preclinical and clinical testing will be essential for addressing these concerns. Developing standardized protocols for exosome isolation, characterization, and functional testing can help mitigate risks and streamline regulatory approval processes. Additionally, using autologous exosomes derived from the patient's own cells may reduce the risk of adverse immune reactions and improve safety [174].

The roles of exosomes in cancer naccines

Cancer vaccines have the potential to stimulate the immune system by activating various cells, particularly T cells. Among the different types of immune cells, several are candidates for exosome-derived vaccines for cancer therapy. For example, B cell-derived exosomes can enhance antigen presentation and improve T cell function, while macrophage-derived exosomes can promote DC maturation and produce pro-inflammatory cytokines [202, 203]. Conversely, cancer-derived exosomes often exhibit immunosuppressive activity. For instance, B cell lymphoma-derived exosomes (BL-Exo) can expand T cells, elevate anti-tumor cytokines, reduce tumor-favoring interleukins such as IL-4 and IL-10, and increase tumor cell apoptosis (Fig. 3) [204, 205].

Recent advancements in exosome-based cancer vaccines have demonstrated their potential in stimulating

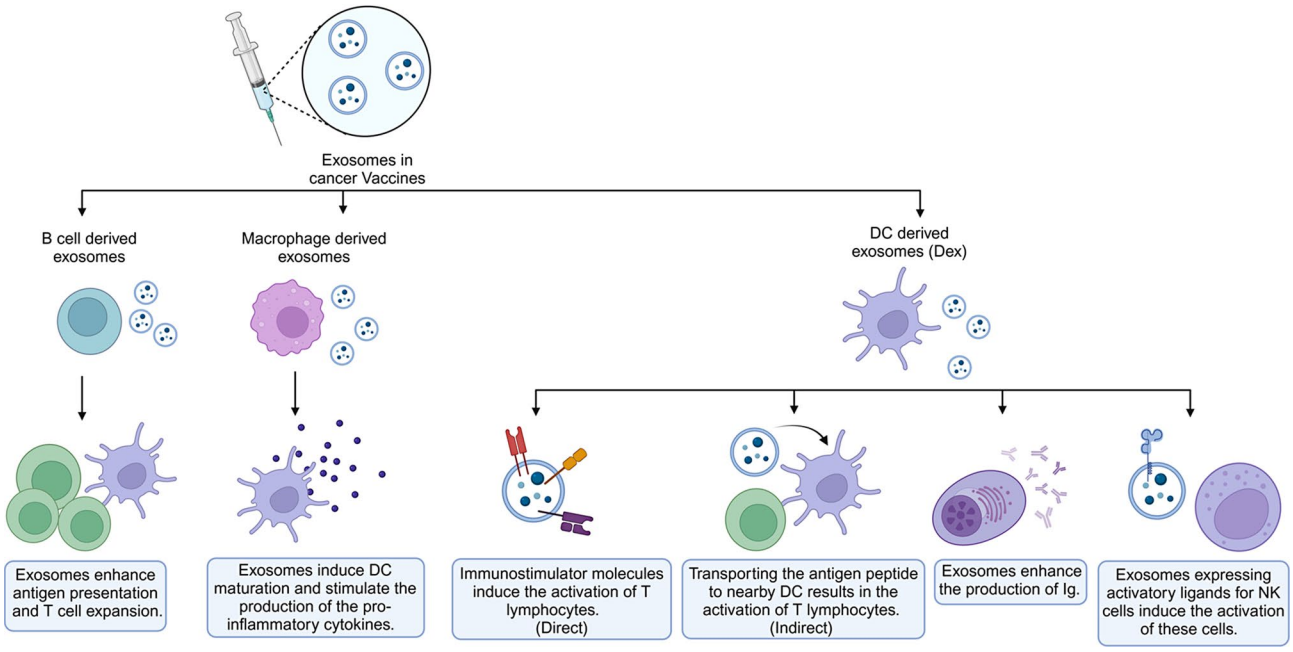

Fig. 3 The Roles of Exosomes in Cancer Vaccines. Cancer vaccines can activate the immune system, especially T cells, using exosome-derived vaccines from B cells, macrophages, and dendritic cells (DCs). These vaccines enhance antigen presentation and promote immune responses. Dendritic cell-derived exosomes (Dex) are particularly effective in delivering tumor-associated antigens and activating T lymphocytes either directly through MHC I and II, CD80, and CD86 expression or indirectly by carrying antigen peptides to bystander DCs. Dex also stimulates B cell immunity by enhancing antibody production and boosts innate immune responses by expressing NKG2D ligands or BAT3 as an NKp30 ligand on the surface for natural killer (NK) cell activation. [The figures were designed by using biorender shapes (https://www.biorender.com)]

strong, targeted immune responses against leukemia and other blood cancers. DC-derived exosomes (Dex), loaded with tumor-associated antigens (TAAs), have been shown to induce robust T cell responses and inhibit tumor growth in preclinical models [158]. Furthermore, recent clinical trials have explored the use of Dex in combination with immune checkpoint inhibitors, leading to enhanced anti-tumor efficacy, particularly in patients with relapsed or refractory AML [158]. The immunostimulatory properties of Dex, combined with their ability to be engineered to carry specific TAAs, provide a novel and highly effective approach to cancer immunotherapy [184]. Additionally, recent studies suggest that exosome-based vaccines can be further enhanced by modifying their surface markers to improve their targeting and uptake by antigen-presenting cells [184].

DC-derived exosomes (Dex) are considered one of the most effective approaches for delivering tumor-associated antigens (TAAs) to stimulate the immune system. Dex offers several advantages over DC-derived vaccines, such as being more controllable, having a longer shelf life, and targeting specific locations more effectively. Dex can activate NK and T cells more efficiently, and when loaded with TAAs, they exhibit enhanced anti-tumor functions in mouse models [206–208]. Among various sources, mesothelioma-derived exosomes are particularly promising for DC-based immunotherapy due to their association with higher survival rates [209]. Structurally, Dex has a bilayer lipid structure rich in phosphatidylinositol and sphingomyelin, contributing to their durability in blood circulation [210]. Dex expresses immune stimulation markers on its surface, such as MHC I and II, CD80, and CD86, which can stimulate and activate T cells. They also express anti-apoptosis proteins like Alix, galectin-3, and thioredoxin peroxidase II [8, 211]. Regarding T cell activation, Dex-induced models are categorized into direct and indirect methods. In the direct model, Dex induces a response through MHC and co-stimulatory molecules on its surface [212]. In the indirect model, Dex carries antigen peptides to bystander DCs, which then stimulate T cells in an antigen-specific manner (Fig. 3) [213].

Dex can also stimulate B cell immunity, as demonstrated by several studies. In one study, mycoplasma-contaminated DC-derived Dex improved immunoglobulin production and activated polyclonal B cell subsets independently of MHC, peptide interaction, or T cell help [214]. Another study showed that Ovalbumin-loaded Dendritic Cell-derived Exosomes (OVA-Dex) accumulated complement factors and elicited a strong IgG response, in addition to B cell activation in mouse models [215]. Furthermore, Dex can evoke innate immune responses. For example, Dex can express NKG2D as an activator receptor on its surface, enhance IL-15Rα, and

promote NK cell proliferation, thereby controlling tumor metastasis [207]. An in vitro study demonstrated that immature DC-derived Dex expresses BAT3 on the surface as an NKp30 ligand for NK activation [216]. Additionally, Dex positively affected invariant Natural Killer T (iNKT) cell proliferation and induced cytokine release from these cells both in vitro and in vivo (Fig. 3) [217].

Challenges and limitations of exosome use for clinical applications

While exosomes hold immense potential as diagnostic and therapeutic agents, significant challenges exist, particularly regarding their large-scale application. One of the key challenges is the scalability of exosome isolation. Standard methods such as ultracentrifugation and size-exclusion chromatography, though effective for small-scale research, do not meet the requirements for clinical-grade production. More advanced methods like tangential flow filtration (TFF) and size-exclusion chromatography (SEC) are being explored to overcome this limitation. However, concerns about exosome purity and yield remain prominent, especially in therapeutic contexts [218–220]. The heterogeneity of exosome populations also poses a challenge. Exosomes derived from different cell types can vary significantly in their cargo and surface markers, leading to inconsistent therapeutic outcomes. Recent efforts have focused on Good Manufacturing Practice (GMP) guidelines for exosome production to ensure better quality control and consistency [221, 222]. This standardization is critical for translating exosome-based therapies into clinical use.

Ethical considerations in exosome research and clinical application

As exosome-based therapies approach clinical reality, several ethical concerns must be addressed. The use of patient-derived exosomes in gene editing or drug delivery raises important questions about informed consent and data privacy. For example, in gene therapy applications, patients must fully understand the potential long-term effects and the heritable consequences of such treatments [223, 224]. Furthermore, exosome-based CRISPR therapies carry risks of off-target effects and ethical implications related to modifying the human genome. Establishing stringent guidelines for the ethical and responsible use of exosome technologies is critical to ensuring patient safety and protecting genetic privacy [225, 226].

Conclusion and future perspective

In conclusion, leukemic exosomes exhibit diverse functions, serving not only as biomarkers for diagnosis but also as crucial means of communication between cells in the bone marrow niche. They play a significant role in the pathogenesis of leukemia by promoting angiogenesis, exerting immunosuppressive effects, and enhancing the invasion and dissemination of malignant cells. Additionally, exosomes derived from leukemic cells can stimulate immune responses, helping the immune system counteract the immunosuppressive conditions commonly associated with malignancies. The origin of the cell from which exosomes are derived is crucial in determining their function; for instance, exosomes from MSCs in the bone marrow microenvironment can contribute to drug resistance due to their immunomodulatory content.

Despite the challenges associated with exosome therapy—such as the large-scale production of clinical-grade exosomes, cost-benefit issues, loading efficiency, limitations in parental cell methods, short in vivo half-life, unsatisfactory blood circulation, rapid clearance, and exosome heterogeneity—some companies have initiated the development of therapeutic exosomes in clinical trials [227, 228]. Recently, three engineered exosomes have entered clinical phases. Tw of these, ExoIL-12™ and ExoSTING™, were developed by Codiak BioSciences. The third, introduced by MD Anderson Cancer Center, involves MSC-derived exosomes loaded with KrasG12D-siRNA for treating metastatic pancreatic cancers with the KrasG12D mutation, currently in a phase I clinical study [229, 230]. Although significant research has been conducted in this field, our understanding of exosomes and their applications is still in its early stages.

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Author contributions
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