Tumour-derived exosomes and their emerging roles in leukaemia (Review)

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Abstract. Exosomes are small vesicles with a diameter of ~40-100 nm that are secreted by the majority of endogenous cells under normal and pathological conditions. They contain abundant proteins, lipids, microRNAs, and biomolecules such as signal transduction molecules, adhesion factors and cytoskeletal proteins, and play an important role in exchanging materials and transmitting information between cells. Recent studies have shown that exosomes are involved in the pathophysiology of leukaemia by affecting the bone marrow microenvironment, apoptosis, tumour angiogenesis, immune escape and chemotherapy resistance. Furthermore, exosomes are potential biomarkers and drug carriers for leukaemia, impacting the diagnosis and treatment of leukaemia. The present study describes the biogenesis and general characteristics of exosomes, and then highlight the emerging roles of exosomes in different types of leukaemia. Finally, the value of clinical application of exosomes as biomarkers and drug carriers is discussed with the aim to provide novel strategies for the treatment of leukaemia.

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1. Introduction

Leukaemia is a common cancer of the haematopoietic system, whose pathogenesis has not been fully elucidated. Leukaemia cells are stagnant in different stages of cell development due to uncontrolled proliferation, impaired differentiation and blocked regulation. They proliferate massively in the bone marrow and other haematopoietic tissues and infiltrate other non-haematopoietic tissues and organs, and these processes are multifactorial and multistage. According to the French-American-British classification standard, leukaemia is divided into four categories: Acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML). If left untreated, these conditions may lead to bone marrow failure and eventual death, and only a few patients are cured, even with the best treatments such as intensive chemotherapy or haematopoietic stem cell (HSC) transplantation (1). With the improvement of treatment technology, especially the progress of HSC transplantation in recent years, the remission rate of patients with leukaemia has been improved, but the majority of patients still experience relapse after remission according to the World Health Organization (WHO) (2).

Exosomes were first discovered in sheep reticulocytes in the 1980s (3). Sheep reticulocytes release vesicles during *in vitro* culture, and the externalization of vesicles was hypothesized to be a specific membrane shedding mechanism, which Johnstone *et al* (4) named 'exosomes' in 1987. Exosomes are vesicles with a diameter of 40-100 nm secreted by living cells under normal and pathological conditions. They have a typical lipid bilayer structure and contain abundant amounts of proteins, lipids, mRNAs or microRNAs (miRNAs/miRs) and present abundantly in the plasma, urine and ascites. They also play important physiological and pathological roles by

interacting with neighbouring or distant cells (5,6). Exosomes mediate the exchange of biological information between cells, which is an important method for tumour cells to transmit information to the outside environment, widely involved in tumour cell proliferation, local invasion and distant metastasis (7,8). Recent evidence indicates that exosomes potential impact the occurrence and development of leukaemia by regulating the bone marrow microenvironment, tumour cell apoptosis, angiogenesis and immune escape (9). The present manuscript aimed to introduce the role of exosomes in the pathogenesis of leukaemia and provide novel strategies for treating leukaemia clinically.

2. Formation and release of exosomes

Extracellular vesicles (EV) are lipid bimolecular membrane vesicles released by cells into the extracellular microenvironment that play an important role in intercellular communication, and also participate in various physiological and pathological body processes. EVs are divided into exosomes, apoptotic bodies, microvesicles and large oncosomes according to their different formation methods. For example, exosomes can be released by almost all cells, transferred to target cells through cell-to-cell communication, and perform numerous biological functions (10). Recently, there has been an increase in research into exosomes, especially in the medical field. The formation of exosomes is a continuous process involving sorted endosomes, intraluminal vesicles (ILV) and intracellular multivesicular bodies (MVB). The cell membrane is invaginated to form a goblet structure when stimulated by microbial attack or stress conditions. Extracellular material or membrane proteins are internalized and form early-sorting endosomes (ESEs), the extracellular cargo enters the cell by cell membrane internalization (for example, via phagocytosis) (11). To participate in the assembly of exosomes, some cargo may enter the cell more efficiently with the help of receptors expressed on the cell membrane. Ubiquitinated molecules such as proteins or RNAs bind to ESEs with the assistance of sorting proteins, and the ESEs gradually mature into late-sorting endosomes (LSEs). ILVs in LSEs are the precursors of exosomes, and LSEs eventually evolve into MVBs. Occasionally, MVBs are degraded after fusion with lysosomes. Or, MVBs fuse with the plasma membrane to release ILVs into the extracellular environment, which are exosomes. Exosomes affect the function of target cells through endocytosis or ligand-receptor recognition (12). The formation process of exosomes is presented in Fig. 1.

Exosome-mediated intercellular communication regulates normal physiological activities between cells and is also widely involved in the pathological process of numerous diseases, including tumorigenesis. Generally, tumour cells can produce more exosomes compared with normal cells, and these tumour-derived exosomes manifest multiple abilities to change the local and distant microenvironment, which contributes to tumorigenesis, metastasis and immune escape (13). Common methods for collecting exosomes from body fluids such as urine, bronchoalveolar lavage fluid, serum and ascites of patients with tumours include ultracentrifugation, ultrafiltration and commercial kits. Each method has advantages and disadvantages. Only the extracted exosomes with high purity, concentration and content while avoiding heterologous protein interference can meet the requirements of subsequent research (14). With the rapid development of modern medical technology, advanced technologies, such as biophysical techniques based on spectroscopy (scanning electron microscopy, atomic force microscopy), and antibody-based techniques (flow cytometry, transmission electron microscopy) can be used to characterise and identified various exosomes (15). A paper-based isotachophoresis technique enables rapid identification of exosomes from healthy cells or tumour cells, and this technique can sensitively detect exosomes down to $2.0\text{-}3.0\text{x}10^{-18}$ M with potential clinical application value (16).

3. Regulatory effect of exosomes on bone marrow microenvironment

The bone marrow microenvironment (BMM) is the basis for the survival of HSCs (17). Increasing evidence indicates that tumour-derived exosomes can remodel the BMM to a leukaemia-favourable microenvironment through the communication of biological information between HSCs and tumour cells (18,19).

AML. The pathogenesis of AML involves a tumour cell favourable BMM, which supports the formation and progression of leukaemia cells, and for exosomes to inhibit the haematopoiesis function of bone marrow through the targeted delivery of miRNAs to haematopoietic progenitor cells (20). AML-derived exosomes that contain coding and non-coding RNAs phagocytosed by bone marrow stromal cells (BMSCs) can promote tumour cell growth by stimulating the secretion of growth factors (21). AML-derived exosomes containing miRNAs that downregulate the expression of retention factors, such as stem cell factor and C-X-C chemokine ligand 12 (CXCL12), in BMSCs may disrupt the haematopoietic function of the bone marrow (22).

AML-derived exosomes inhibit the expression of haematopoietic factor Dickkopf-related protein 1 (DKK1) and HSC support factors, such as CXCL12, kit ligand and insulin-like growth factor I, in the bone marrow. This forms a favourable tumour cell microenvironment and impairs the haematopoiesis ability of bone marrow (23). The loss of the haematopoiesis ability in patients with AML is partly attributable to AML-derived exosomes transporting miRNAs to HSPCs, which inhibit the C-MYB gene function through miR-150 and miR-155, and inhibit the clonogenic ability of myeloid cells (24). Exosomes containing miR-4532 released by AML cells interact with HSCs and impair the clonogenic ability of HSCs through the JAK2 and STAT3 signalling pathways, inhibiting bone marrow haematopoiesis by increasing the expression of haematopoietic inhibitor DKK1 (25). Exosomes containing miR-7977 released by AML cells can enhance the proliferation ability of BMSCs through the Hippo-YAP signalling pathway, which may be involved in the upregulation of leukaemia-supporting stroma growth (26). A recent study confirmed that the expression level of miR-425-5p is reduced in patients with $CD34^{+}CD38^{-}$ AML, and exosomes containing miR-425-5p derived from the BMSCs of these patients can inhibit AML cell proliferation, invasion and migration through the Wilms tumour 1 associated protein pathway, this indicates

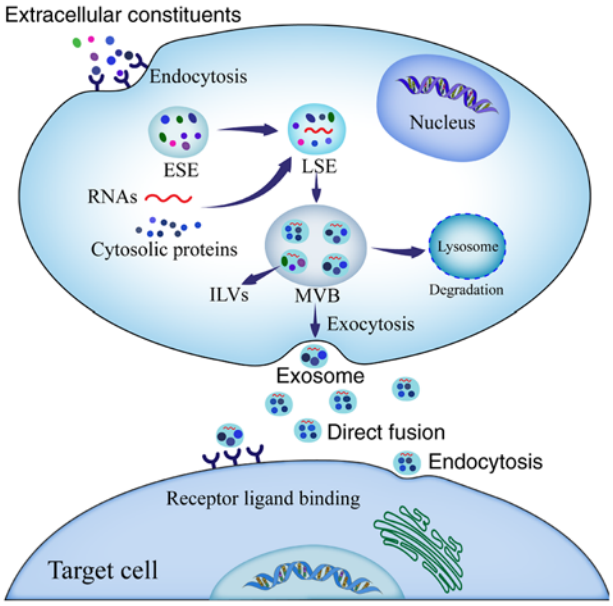

Figure 1. Biogenesis of exosomes. The ESE forms from the invagination of the plasma membrane to surround macromolecules within the extracellular environment. Intracellular proteins and RNAs are packaged into the ESE with the assistance of sorting proteins and form ILVs, which are the precursors of exosomes, and ESE gradually matures into LSEs. LSEs eventually evolve into MVBs. Fusion of the MVB with the plasma membrane releases exosomes into the extracellular milieu in an exocytic process. ESE, early-sorting endosome; ILV, intraluminal vesicle; LSE, late-sorting endosomes; MVB, multivesicular bodies.

that miR-425-5p may be a potential therapeutic target for patients with AML (27).

ALL. Tumour-derived exosomes are important messengers in leukaemia that remodel the BMM into a malignant ecology to improve support for ALL cell survival through inflammatory cytokines, chemokines and adhesion molecules. Abnormal production of inflammatory mediators in bone marrow may reduce the normal function of HSCs during the tumorigenesis of ALL. Exosomes secreted by tumour cells contain miRNAs, such as miR-146a-5p, miR-181b-5p and miR-199b-3p, that bind to Toll-like receptor (TLR)8 on the surface of bone marrow mesenchymal stromal cells (BM-MSCs). This activates inflammatory pathways and remodels the tumour microenvironment (TME) through TLR8 signalling, significantly reducing the haematopoietic capacity of normal HSCs and promoting the progression of ALL (28,29).

CLL. The pathogenesis of CLL is closely associated with the BMM, which supports tumour cell growth and a dysfunctional immune system. The interaction of BMSCs with CLL-derived exosomes induces the expression of a cancer-associated fibroblast phenotype, and exosome-stimulated BMSCs exhibit an enhanced proliferation and inflammatory cytokine secretion ability. This is favourable for creating a microenvironment that supports tumour cell survival (30). Furthermore, the endocytosis of exosomes by endothelial cells increases angiogenesis *in vitro* and *in vivo* and promotes tumour cell metastasis (31). A study suggested that B cell receptor (BCR) signalling can promote CLL pathogenesis and tumour cell survival. MiR-150 and miR-155 expression levels are significantly elevated in CLL-derived exosomes by α-IgM stimulation, promoting disease progression; however, the tyrosine kinase inhibitor (TKI) ibrutinib may offset this effect (32). CLL-derived exosomes regulate the dynamic interaction between tumour cells and the bone marrow microenvironment, and regulate the TME through NF-κB and the PI3K/AKT pathway, providing support for the pathogenesis of CLL (33).

CML. Exosomes released by CML cells stimulate BMSCs to produce pro-inflammatory chemokines, such as IL-8, that promote the expression of malignant phenotypes of CML cells through C-X-C chemokine receptor signalling (34). Exosomes released from CML cells contain miRNAs that promote the formation of the TME. Among the 124 miRNAs identified from the CML cell line LAMA84, miR-126 can down-regulate the expression levels of chemokine CXCL-12 and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, This impairs the adherence of tumour cells to endothelial cells, which may facilitate tumour cell migration from the bone marrow and dissemination *in vivo* (35).

A recent study showed that K562 cell-derived exosomes transfer miR-711 into BMSCs, inhibiting the adhesion ability of BMSCs by down-regulating CD44 molecule expression. There is a significantly higher level of miR-711 in exosomes derived from K562 cells compared with exosomes derived from parental cells (36). The BM-MSCs co-cultured with exosomes derived from K562 cells showed a lower adhesion rate, which may be associated with tumour cell metastasis. Hyperleukocytic acute leukaemia patient-derived exosomes contain miR-125b, which can reduce colony forming units and the expression of BM-MSC haematopoietic-related factors α-globulin, γ-globulin, colony-stimulating factor 2, CRTX4 and CXCL12. These results indicated that exosomes carrying miR-125b might affect the haematopoietic differentiation function of HSCs and the haematopoietic support for BM-MSCs (37).

CML-derived exosomes containing miR-320 can be endocytosed by the adjacent BMSCs and then inhibit the function of osteoblasts at least partially via β-catenin, which contributes to CML progression. Notably, β-catenin is a key regulator of osteogenesis that can promote the maturation of osteoblastic precursor cells into mature osteoblasts through Wnt signalling, the 3'-UTR of β-catenin contains a binding site that miR-320 can recognize (38). K562 cell-derived exosomes induce T cell fate to evolve toward tumour-favourable suppressor T cells instead of traditional killer T cells by promoting the expression of NAD (P)H quinone oxidoreductase 1, programmed death ligand 1 (PD-L1) and forkhead box protein P3 (FOXP3), while increasing the secretion of cytokines such as IL-10, IL-6 and IL-17 (39).

Cancer-associated cachexia (CAC) impacts the quality of life of patients with CML, especially in the advanced stage. It has been confirmed that mice significantly lost weight and body fat percentage after being injected with CML-derived exosomes (40). Further research confirmed that the adipogenic ability of adipose-derived stem cells are reduced by exosomes containing miR-92a-3p, indicating that tumour-derived exosomes may be involved in the

Table I. Regulatory effects of exosomes on the bone marrow microenvironment.

First author, year	Cancer type	miRs in exosome	Effects	(Refs.)
Hornick *et al*, 2016	AML	miR-150, miR-155	Suppresses haematopoiesis of haematopoietic stem and progenitor cell	(24)
Zhao *et al*, 2019	AML	miR-4532	Decrease the clonogenic and haematopoietic function in haematopoietic stem cells	(25)
Yoshida *et al*, 2019	AML	miR-7977	Enhance the proliferation ability of bone marrow mesenchymal stem cells	(26)
Zhang *et al*, 2021	AML	miR-425-5p	Inhibit AML cell proliferation, invasion migration ability, and induce cell apoptosis	(27)
Rios *et al*, 2022	ALL	miR-146a-5p, miR-181b-5p, miR-199b-3p	Promotes the formation of the tumour microenvironment and reduces the haematopoietic ability of haematopoietic stem cells	(29)
Yeh *et al*, 2015	CLL	miR-150, miR-155	Regulate the pathogenesis of CLL through BCR signalling	(32)
Taverna *et al*, 2014	CML	miR-126	Downregulate CXCL12 and VCAM1 expression on endothelial cells and promote leukaemia dissemination	(35)
Jiang *et al*, 2020	CML	miR-711	Suppress the adhesive function of bone marrow mesenchymal stem cells	(36)
Yang *et al*, 2021	CML	miR-125b	Regulate the haematopoietic differentiation function of HSC and the haematopoietic support function of BM-MSC	(37)
Gao *et al*, 2019	CML	miR-320	Inhibit osteoblast function and remodel the bone marrow niche	(38)
Wan *et al*, 2019	CML	miR-92a-3p	Attenuate adipogenesis of adipose-derived mesenchymal stem cells and promote CAC progression	(40)

AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; BCR, B cell receptor; VCAM-1, Vascular cell adhesion molecule 1; BM-MSC, bone marrow mesenchymal stromal cells; CAC, cancer-associated cachexia; CXCL12, chemokine (C-X-C Motif) ligand 12; miR, microRNA.

occurrence of CAC (40). The regulatory effects of exosomes on the bone marrow microenvironment are presented in Table I.

4. Effects of exosomes on proliferation and apoptosis of leukaemia cells

AML-derived miR-5195-3p can simulate tumour cell proliferation by activating the cell cycle, and can also improve the anti-apoptotic ability of tumour cells by down-regulating Bcl-2 and up-regulating Bax expression. However, AML-derived miR-23b-5p can reduce tumour cell proliferation and induce apoptosis via the PI3K/AKT pathway (41,42). BMSCs-derived miR-7-5p inhibits AML cell proliferation and promotes apoptosis through PI3K/AKT/mTOR signalling, indicating that these miRNAs may be potential therapeutic targets for AML treatment (43). BM-MSCs derived exosomes that contain miR-222-3p can inhibit AML cell line THP-1; however, these effects of BM-MSCs exosomes are reduced when the IRF2/inositol polyphosphate 4-phosphatase type II (INPP4B) signalling pathway is blocked, which suggests that BM-MSCs regulate THP-1 cells proliferation and apoptosis through IRF2/INPP4B signalling, which may provide novel therapeutic strategies for AML (44).

A study confirmed that miRNA-181b-5p is highly expressed in ALL cell lines, and exosomes carrying this miRNA can

promote the proliferation, migration and invasion ability of ALL cells. MiRNA-181b-5p can also promote the progression of ALL by inhibiting cell apoptosis (45). CML-derived exosomes can promote the proliferation ability of tumour cells through TGF-β1 signalling in a CML mouse xenograft model while promoting the expression of BCL-w, BCL-xl and survivin to resist apoptosis (46). Adult T cell leukaemia/lymphoma (ATL) is a haematological disease in which lymphocytes proliferate abnormally in the bone marrow, and human T-lymphotropic virus type 1 (HTLV-1) is the causative agent. Lymphocytes will release exosomes containing viral Tax proteins, pro-inflammatory mediators and viral mRNA transcripts after being infected by HTLV-1, which can improve the survival of leukaemia cells by inhibiting Fas expression through AKT signalling, further studies confirmed that this effect depends on the anti-apoptotic protein cFLIP (47). Paediatric acute lymphoblastic leukaemia (pALL) is a malignancy of the lymphoid line of blood cells that accounts for a large percentage of all childhood leukaemia cases. Exosomes isolated from patients serum containing miR-181a, which can promote disease progression by upregulating proliferation genes (e.g. PCNA, Ki-67) and survival genes (e.g. MCL-1 and BCL2). Specific inhibition of miR-181a can reverse pALL exosome-induced proliferation function of leukaemia cells *in vitro*, suggesting miR-181a may be a therapeutic target for pALL (48). These findings highlight the effects of exosomes on the proliferation and apoptosis of leukaemia cells which may provide novel ideas for the treatment of leukaemia.

5. Effects of exosomes on leukaemia angiogenesis

The formation of new blood vessels contributes to the development of malignant tumours. Exosomes circulate freely in body fluids, accumulate in the TME and promote tumour angiogenesis (49). Exosomes deliver angiogenesis-promoting molecules and genetic agents to recipient cells, and are responsible for reprogramming the phenotype and function of endothelial cells in the TME, promoting leukaemia progression (50).

CML-derived exosomes stimulate vascular endothelial cell proliferation and promote the formation of new blood vessels through Src signalling in CML angiogenesis. Tyrosine kinase inhibitors dasatinib and imatinib (IM) can significantly inhibit the secretion of exosomes and the proliferation of the human umbilical cord endothelium *in vitro*. A further study confirmed dasatinib can attenuate angiogenesis induced by exosomes in a Matrigel mouse embolization model, CML cell-derived exosomes could induce angiogenic activity in human umbilical vein endothelial cells (HUVECs), and dasatinib manifested an inhibitory effect on exosome through Src signaling (51).

Exosomes isolated from the blood of patients with CML have been reported to contain amphiregulin which can activate the epidermal growth factor receptor signalling of BMSCs, increasing the expression of MMP-9 and IL-8, promoting the adhesion of leukaemia cells to stromal cells, supporting the development of disease (52). The progression of CML is often associated with increased angiogenesis, and CML-derived exosomes can induce the proliferation and angiogenesis of human umbilical vein endothelial cells via miR-92a (53). The exosomes secreted by K562 cells can promote the expression of VEGFR and the formation of new blood vessels, and anti-angiogenic gold nanoparticles can attenuate the pro-angiogenic effect of exosomes, highlighting nanomedicine-based potentiality to prevent the spread of leukaemia cells (54).

A hypoxic environment can regulate tumour angiogenesis. Exosomes released from K562 cells cultured in a hypoxic (1%) environment were more prone to induce tumour angiogenesis via miR-210 compared with those cultured in normoxic (20%) conditions by downregulating angiogenesis inhibitory factor ephrin-A3, which is essential for tumour cell survival in hypoxic environments (55). Exosomes secreted by K562 cells that contain miR-92a can promote tumour angiogenesis under hypoxic conditions through targeted inhibition of hypoxia-inducible factor 1 by miR-135b (56). Exosomes released from CML cells contain miR-21, which can increase expression levels of IL-8 and VCAM-1 and promote tumour angiogenesis. A vascular network formation assay confirmed that curcumin-treated exosomes induce the secretion of proteins with antiangiogenic activity and attenuate the angiogenic ability of exosomes (57). A previous study has indicated that AML-derived exosomes contain miRNAs for VEGF and VEGFR expression, promoting HUVEC cell proliferation and vascular remodelling while resisting apoptosis by promoting HUVEC cell glycolysis (58). These findings may contribute to developing novel therapeutic strategies for AML.

CLL-derived exosomes can activate the AKT signalling pathway in BMSCs following activation of cyclin D1, which produces vascular endothelial growth factor, providing a 'homing and nurturing' microenvironment for tumour cells and promoting CLL progress (59). Exosomes released by ATL cells containing angiogenic factors act on vascular endothelial cells to create a favourable angiogenesis microenvironment for tumour cells. Tumour cells of patients with ATL release exosomes containing miR-21, miR-155 and vascular endothelial growth factor, which interact with MSCs and induce the activation of the NF-κB signalling through Tax protein, this activates leukaemia related genes and angiogenic genes that regulate the properties of MSCs and promote leukaemia progression (60). These findings may provide novel ideas for treating haematological malignancies.

6. Effects of exosomes on tumour cell immune escape and vaccine development

The immune escape of tumour cells is one of the important reasons for the rapid progression of leukaemia. Leukaemia cells evade the supervision of the immune system by down-regulating the expression level of tumour antigens and releasing immune inhibitory cytokines to inhibit the function of lymphocytes (61).

NKG2D is a common activating receptor that is abundantly expressed on NK cells, NKT cells and $CD8^+$ CTL cells, which plays an immune surveillance role for tumour cells, and the abnormal loss of NKG2D may be an important reason for tumour cell immune evasion (62). Exosomes secreted by tumour cells can down-regulate NKG2D expression in NK cells and $CD8^+$ T cells while promoting the expression of TGF-β1 in tumours, creating an inhibitory immune microenvironment for tumour cell growth. Szczepanski *et al* (63) have confirmed that AML-derived exosomes can reduce the

expression level of NKG2D and weaken the killing ability of NK cells, sera from patients with acute myeloid leukaemia contained elevated levels of TGF-β, neutralizing anti-TGF-β antibodies inhibited exosome-mediated suppression of natural killer cell activity and NKG2D down-regulation. RNA hY4 is a highly abundant non-coding RNA that is enriched in exosomes derived from the plasma of patients with CLL (64). RNA sequencing and proteomic analysis has revealed that hY4 is a driver for TLR7 signalling and promotes inflammatory cytokines such as CCL2, CCL4 and IL-6 release along with up-regulated PD-L1 expression. This contributes to tumour-associated inflammatory responses and immune escape, indicating that regulation of exosome-mediated inflammatory response may provide novel ideas for the treatment of CLL. Tumour-derived exosomes contain NKG2D ligands (MICA/B, ULBP1-6) that can bind to NKG2D competitively, impairing the monitoring ability of NK cells to tumour cells (65). AML-derived exosomes down-regulate naive $CD4^+$ T cell activation, mediate Fas/FasL-driven T cell apoptosis, promote $CD4^+CD25^+FOXP3^+T_{reg}$ cell activation and mediate tumour cell immune escape (66,67).

However, certain tumour-derived exosomes can induce specific antitumour immune responses and are expected to develop as a promising tumour vaccine. Dendritic cells (DCs) have numerous dendritic or pseudopodia-like protrusions that stretch out when they mature, and they have a powerful antigen-presenting function in the body. DC cells can recognize invading pathogens effectively, present antigens peptides to T cells and activate the adaptive immune responses, resulting in anti-pathogen immune reactions (68). Mature DCs produce exosomes that elicit potent immune activation, resulting in tumour eradication and bacterial or virus elimination. Notably, DC cells are closely associated with the pathogenesis of tumours. The $CD8^+$ CTL-mediated immune response initiated by DCs is an important component of antitumour immunity and the basis for DC cell immunotherapy (69). In a previous study, the autologous monocytes of the patient were extracted and induced to mature DCs *in vitro* and loaded with tumour antigens to generate tumour antigen-loaded DCs; these DCs were then injected into the patient to activate the lymphocytes, which stimulated an antitumour immune response (70,71). The specific mechanism of DC cell immunotherapy is shown in Fig. 2. Numerous DC-based immunotherapies have been developed and have produced satisfactory treatment effects in certain clinical trials (72,73). Targeted delivery of antigens to DCs via exosomes represents a potential candidate approach for DC vaccines, which demonstrate convincing therapeutic effects in myeloma cells, liver cancer and breast cancer cells *in vitro* (74-76). Exosomes from TGF-β1-silenced L1210 cells (LEXTGF-β1si) can reduce the expression level of TGF-β1 in DCs and promote the maturation of DCs significantly. The matured DCs activate CD4+ T cells, and the subsequent tumour-specific CTL responses include killing responses and inflammatory responses, suggesting that targeting DCs via LEXTGF-β1si may be a promising immunotherapy strategy (77).

A previous study down-regulated PD-L1 expression in leukaemia cell exosomes using PD-L1 short hairpin RNA, and then compared the capacity of exosomes derived from PD-L1-silenced acute lymphocytic leukaemia-derived cells (LEXPD-L1si) and non-modified exosomes to induce anti-leukaemia immunity. The results confirmed that LEXPD-L1si improved DC maturation and subsequently Th cell proliferation and cytokine release while influencing the killing ability of CTL cells.The following *in vivo* experiments confirmed that LEXPD-L1si vaccination inhibits tumour growth and significantly prolongs the survival rate of mice (78). Exosomes can affect the antitumor ability of the body by regulating PD-L1 expression and the down-regulation of PD-L1 by exosomes induces anti-leukaemia immunity, which demonstrates the potential application of this therapy in leukaemia immunotherapy (79,80). These findings provide evidence for a novel exosome-mediated mechanism in leukaemia, and the specific effects of exosomes on tumour cell immune escape require further in-depth research.

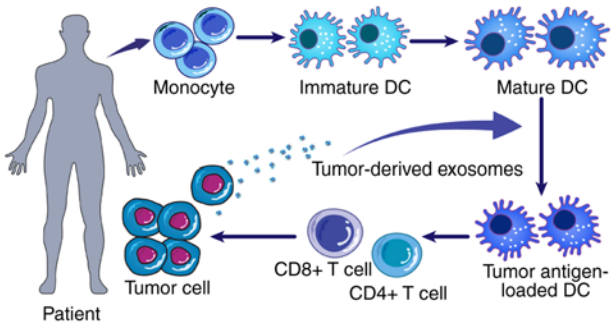

Figure 2. Process of immunotherapy using leukaemia cell-derived exosomes as inciting antigens. Monocytes are harvested from patients with leukaemia and differentiated into immature DCs and mature DCs. Mature DCs are pulsed with leukemic exosomes which contain leukaemia patient-specific antigens. The tumour antigen-loaded DCs display leukaemia antigens and induce a target-specific immune response by activating $CD4^+$ T cell and $CD8^+$ T cell, inducing a target-specific immune response to tumour cells. DC, dendritic cells.

7. Exosomes and drug resistance

Leukaemia chemotherapy resistance means leukaemia cells are insensitive or resistant to chemotherapy drugs. Drug resistance may lead to the recurrence of leukaemia and cause treatment failure, which are also the main points and difficulties of treatment for leukaemia.

Although there had been a rapid development of novel therapies for leukaemia, minimal residual disease (MRD) is still responsible for relapse and drug resistance. MRD is an obstacle to the treatment of leukaemia. Galectin-3 may play an important role in the MRD process by promoting the anti-apoptotic, colony formation and cell drug resistance abilities of tumour cells (81). Studies have confirmed that BM-MSCs can up-regulate the expression level of Galectin-3 in ALC cells, activate the Wnt/β-catenin signalling pathway and promote the progress of drug resistance in tumour cells (82). BMSCs of the B cell precursor from patients with acute lymphoblastic leukaemia (pre-B ALL) can encapsulate Galectin-3 in exosomes and deliver it to B-ALL cells, inducing drug resistance to nilotinib and vincristine by activating NF-κB signalling. Galectin-3 may be a potential target to counteract the protective effect of BMSCs on tumour cells (83).

Exosomes secreted by AML cells contain heat shock protein 70 and lysosome-associated membrane protein 3, which contribute to the interaction between AML and BMSCs. These proteins protect AML cells from apoptosis induced by the chemotherapeutic drug, etoposide, while reducing the sensitivity of AML cells to chemotherapeutic drugs by promoting the production of IL-8 (84). The interaction between AML and BMSCs contributes to a protective environment for tumour cell development and resistance to chemotherapeutics (85), BMSC-secreted exosomes protect AML cells from Ara-C-induced cytotoxicity, and this chemoresistance is closely related to the decrease in nucleoside transporter activity from the cell surface. The progression of patients with AML is often accompanied by a FMS-like tyrosine kinase 3 (Flt3) mutation, and several chemotherapeutic drugs targeting FLT3 mutations have achieved satisfactory clinical treatment effects (86,87). Exosomes released by BMSCs of AML patients protect tumour cells by resistance to AC220 (a FLT3 kinase inhibitor) therapy, which is associated with miRNA-155 and miRNA-375 carried by exosomes (88). However, the specific mechanism has not been clearly understood. Another study confirmed that AML-derived exosomes containing miR-10a can target regulation of nuclear pre-MRNA domain-containing 1A and activate Wnt/β-catenin signalling to reduce the sensitivity to cytarabine of leukaemia cells (89).

BMSC-derived exosomes reduce spontaneous apoptosis of CLL cells and increase chemoresistance to fludarabine, ibrutinib, idelalisib and vegetate; in addition, the migratory capacity of CLL cells is also increased (90). Previous studies have confirmed fibroblast growth factor 2 (FGF2) is highly expressed in BMSCs and AML. Studies showed that exosomes are secreted by BMSCs containing FGF2, which are endocytosed by leukaemia cells and protect tumour cells from the chemotherapeutic agents TKIs, blocking the effects of FGF2 on stromal cells can reduce exosome release, indicting inhibition of FGF2 may be a therapeutic option for tumour resistance to TKIs (91,92). IM is a common TKI that is widely used in CML and can significantly improve the survival rate and quality of life of patients with CML. However, it has been shown that exosomes are closely associated with IM resistance; proteomic analysis of exosomes showed that 151 proteins were up-regulated and 128 proteins were down-regulated in the exosomes of patients who were IM-resistant compared with patients with CML who were IM-sensitive (93). Further bioinformatical analysis has shown that ribosomal protein RPL13 and RPL14 are notably up-regulated in IM-resistant patients with CML, and proteomic analysis of exosomes may provide novel ideas for treating IM resistance (93).

IM serves an important role in CML treatment and IM resistance is also an obstacle to CML treatment. A previous study showed that ubiquitin-specific protease is significantly up-regulated in IM-resistant clinical samples; miR-146a-5p down-regulated the IM resistance of CML, human umbilical cord mesenchymal stem cell-derived exosomes can promote IM-induced apoptosis through miR-145a-5p/USP6,indicating the potential role of miR-146a-5p in leukaemia chemoresistance (94). A study has confirmed that miR-328 is significantly decreased in IM-resistant patients, where overexpression of miR-328 sensitizes drug-resistant tumour cells to IM. By contrast, knockdown of miR-328 confers IM resistance in tumour cells, and targeting delivery exosomes can increase expression of miR-328 and increase tumour cell sensitivity to IM (95). MiR-365 in exosomes of CML cells is closely associated with IM resistance of tumour cells. CML cells that receive an exosomal delivery of miR-365 show a lower chemosensitivity and apoptosis rate, and miR-365 can induce chemoresistance in tumour cells by inhibiting the expression of pro-apoptotic proteins (96). An *in vitro* study has confirmed that combining exosomes secreted by human umbilical cord mesenchymal stromal cells with IM in K562 cells can enhance the expression of IM-induced Bax expression through caspase-3/9 signalling, which promotes tumour cell apoptosis and increases the sensitivity of tumour cells to IM (97). Therefore, combining IM with exosomes may be a potential strategy for tumour cell drug resistance. These findings highlight the role of exosomes in tumour cell drug resistance, and regulating miRNA expression through exosomes may provide new ideas for overcoming drug resistance in leukaemia treatment. The roles of exosomes in the pathogenesis of leukaemia are summarised in Fig. 3.

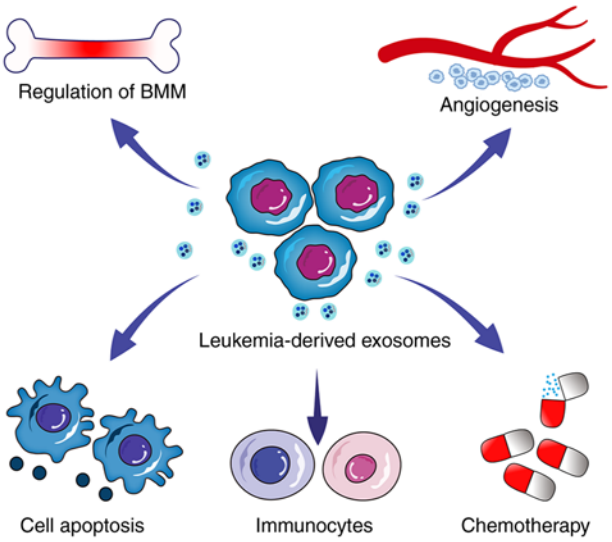

Figure 3. Roles of tumour-derived exosomes in leukaemia. Exosomes are involved in the pathophysiology of leukaemia by affecting the bone marrow microenvironment, tumour angiogenesis, tumour cell apoptosis, immune escape and chemotherapy resistance.

8. Exosomes as biomarkers for leukaemia

The potential function of exosomes is far beyond immunology, neurobiology, stem cell science and oncology. Notably, exosomes have a far-reaching impact on tumour cell pathogenesis, immune escape, cell proliferation and chemoresistance. For a long time, exosomes have been hypothesised to be involved in the whole process of tumour metastasis although the specific effects are still unknown and controversial (98).

In recent years, exosomes have received more attention as a promising tumour screening, diagnostic and prognostic biomarker. Bioactive molecules packaged in exosomes can promote tumour cells remodelling the microenvironment, targeting distant cells and promoting cancer metastasis. The biological agents such as miRNA in exosomes are stably and abundantly present in the body, and extracellular enzymes

will not readily degrade them, this makes exosomes potentially become tumour cell biomarkers (99). Molecular and genetic analysis of exosomes in leukaemia patients may potentially provide a prognosis for patients and provide new strategies for clinical treatment (100-102). Exosomes from AML tumour cells can be used as a biomarker for AML treatment, as patients who achieved remission and survived at 3-year follow-up had significantly lower exosome levels compared with deceased patients. Therefore, specific proteins and miRNAs in exosomes can be used to trace the presence of MRD and guide doctors to adjust treatment strategies on time (103,104). Exosomes isolated from the plasma of patients with AML contain TGF-β1, which inhibits the cytotoxicity of NK cells (105). Changes in exosomes may reflect the response of a patient with AML to chemotherapy, and the exosomal profile may suggest the presence of residual disease in patients considered to have achieved complete remission. MiR-125b in AML-derived exosomes can target the BAK1 gene, inhibit tumour cell apoptosis and promote the pathogenesis of AML. The elevated miR-125b levels indicate patients are at higher risk of relapse and death, and so miR-125b levels may be a prognostic indicator for AML (106,107).

A study detected the content of exosomal miR-532 in 198 patients with AML and revealed that up-regulation of miR-532 is negatively correlated with energy metabolism such as fructose and glutamine in tumour cells. Patients with high expression of miR-532 had an improved overall survival rate, indicating that miR-532 may be used as a predictor of survival in patients with AML (108). Non-coding RNAs in exosomes support the pathogenesis of CLL, and miR-155 is overexpressed in monoclonal B lymphocytosis (MBL), which may potentially promote the transition of MBL to CLL (109). MiR-155 can be used as a biomarker for the risk of progression in individuals with MBL, as well as to identify patients with CLL who may not respond well to therapy. MiR-150 is highly expressed in CLL patients compared with healthy subjects, and the expression level of miR-150 is associated with tumour burden, disease aggressiveness and poor prognostic factors. Patients with low cellular miR-150 or patients with a high serum miR-150 level have a shorter treatment-free survival (TFS) and overall survival (OS); therefore, miR-150 may be able to monitor for disease progression as well as be an indicator for CLL prognosis (110). CML is a malignant proliferation driven by a characteristic fusion gene called BCR-ABL. The U.S. Food and Drug Administration has approved TKIs for treating CML considering their satisfactory therapeutic effect in the majority of patients (111). Monitoring BCR-ABL-derived exosomes using digital PCR after TKI therapy can identify active tumour cells and guide the follow-up treatment strategies for CML patients (112,113). These results show that exosomes can provide prognostic judgement on patients with leukaemia and new strategies for clinical treatment as an important biomarker. However, the specific mechanism remains to be further invested.

9. Exosomes as drug carriers for leukaemia

Exosomes are small intracellular membrane-based vesicles similar to the cellular components of the body, and this non-immunogenic drug delivery vehicle has advantages compared with traditional drug delivery systems, such as liposomes or nanoparticles (114). The unique biocompatibility, tissue specificity, high stability, tumour homing ability and tuneable targeting efficiency confer exosomes as an attractive drug delivery system with potential application in tumour therapy (115). BCR-ABL fusion protein promotes CML pathogenesis and IM is a selective inhibitor of BCR-ABL; exosomes loaded with IM or BCR-ABL siRNA can target CML cells and inhibit cancer cell growth by interacting with IL-3 receptors on tumour cell surface, alleviating drug resistance and adverse reactions during treatment (116). Curcumin can inhibit the expression of BCR-ABL in CML cells through exosome-derived miR-21 and inhibit the growth of tumour cells, suggesting that packaging miR-21 in exosomes may contribute to the antileukemic effect of curcumin in CML (117). Tumour cell-derived exosomes carry tumour-associated antigens that can stimulate DC cell activation and induce immune responses, CD11c, MHCII and IL-12 are up-regulated in exosome-loaded DC cells and activate $CD4^+$ T cells effectively, prolonging the survival time of WEHI-3B mice (myelomonocytic leukaemia mice) significantly, exosomes enriched from patient sera are likely to provide an optimized source of individual-specific antigens for DC loading and vaccination, considering that exosomes are abundant in the serum of tumour patients (118). High expression levels of epidermal growth factor receptor (EGFR) contribute to the rapid progression of tumours, and is involved in tumour invasion and metastasis. A novel class of exosomes called synthetic multivalent antibodies retargeted exosomes (SMART-Exos) is generated in this situation. These SMART-Exos contain two different antibodies that can simultaneously target EGFR on tumour cells and CD3 receptors on T cells. Further in-depth study confirms SMART-Exos show tight binding ability to both EGFR-expressing triple-negative breast cancer MDA-MB-468 cells and T cells, which demonstrated satisfactory antitumour activity by activating T cells to attack breast cancer cells. SMART-Exo may likely be adapted for other disease models by utilizing different types of functional antibodies (119). Cancer cell-derived exosomes were engineered to carry DOXIL (doxorubicin HCl liposome injection) and injected into HT1080 tumour-bearing nude mice. These drug-loaded exosomes showed an enhanced therapeutic effect and more effective clearance of tumour cells in mice compared with the DOXIL alone group (120). These studies provides new strategies for exosome-based targeted delivery of antitumour drugs.

10. Summary and perspectives

Increasing studies have confirmed that tumour-derived exosomes can affect the pathogenesis and development of leukaemia by affecting the bone marrow microenvironment, apoptosis, angiogenesis, chemoradiotherapy resistance and immune escape. Certain exosome-based therapies are now used for clinical or research purposes with an in-depth understanding of the physiological and pathological roles of exosomes, although exosome-related technical and regulatory issues remain to be resolved. Notably, exosomes can be used as a biomarker to monitor leukaemia progress and as a carrier to

transport chemotherapeutic drugs to inhibit the development of leukaemia, demonstrating the potential of exosome-based intervention ability in leukaemia. Notably, there need to be unified standards regarding the efficiency and drug delivery of exosomes, which are the challenges exosomes face. However, in-depth research is needed on the specific mechanism of exosomes in tumour cells, such as how obtaining high-purity exosomes for treatment and accurate delivery is particularly important, and correlational research which may impact leukaemia treatment. The following study on exosomes should focus on solving the problems of tumour cell drug resistance and recurrence, considering a significant proportion of patients relapse after treatment. In conclusion, exosomes demonstrate potential value in diagnosing leukaemia and treating and monitoring disease development. Therefore, a complete understanding of the specific mechanism of exosomes in leukaemia may provide new ideas and strategies for future clinical treatment.

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Authors' contributions

DLD conceived and designed this review. LC and TX wrote the first draft. BW participated in writing of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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