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REVIEW

Extracellular Vesicles in Acute Myeloid Leukemia: Biology, Diagnostic Applications, and Therapeutic Potential

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ABSTRACT: Acute Myeloid Leukemia (AML) is one of the most complex hematological malignancies associated with the rapid production of immature myeloid cells and poor prognosis, even with the development of therapeutic options. Exosomes, which are extracellular vesicles with sizes ranging from 30 to 150 nm, have drawn a lot of interest because of their capacity to carry molecular cargoes, including DNA, mRNA, and non-coding RNAs. Various cells produce these vesicles, which have been shown to effectively transport their molecular contents to target cells via a variety of bodily fluids. This review comprehensively discusses the importance of extracellular vehicles (EVs) in AML development, diagnosis, and therapy. Small extracellular vesicles (sEVs) and exosomes are involved in the intercellular communication in the BM microenvironment and modulate disease development, resistance to therapy, and treatment outcomes. Recent development has shown that they could be regarded as minimally invasive diagnostic markers, especially for the detection of minimal residual disease (MRD) and response to treatment. This review summarises current knowledge on EV biology in AML and discusses their diagnostic and therapeutic potential, along with technical issues and perspectives of the field.

KEYWORDS: Extracellular vesicles (EVs); Acute Myeloid Leukemia (AML); exosomes; microRNA (miRNA); tumour microenvironment; minimal residual disease (MRD)

1 Introduction

Acute Myeloid Leukemia (AML) is a highly aggressive disease that affects the BM and PB by the excessive production of immature myeloid cells called myeloblasts. These myeloblasts do not mature as required, consequently altering the normal hemopoiesis process and hindering the formation of normal blood cells, and hence the clinical features including anemia, infection, and haemorrhagic proclivity [1]. While treatments such as chemotherapy and stem cell transplantation can effectively produce remission, numerous patients experience relapse or resistance; therefore, new approaches to diagnosis and treatment are required [2].

Extracellular vesicles (EVs) have recently been identified as important players in AML development and prognosis [3]. EVs are membranous structures that are secreted by nearly all cell types, including leukemic cells, and are made up of lipids, nucleic acids, and proteins [4]. They are involved in short- and long-range signalling, both intercellular and intracellular. Originally, EVs were described as procoagulant platelet-derived particles in the mid-1940s, and in the subsequent years, they were found in different body fluids. Not until the 2000s was it realized that EVs are enriched with RNA molecules, including microRNA (miRNA), which play an important role in cell signalling and disease development [5]. EVs are now known to be secreted by most cell types and are present in numerous body fluids, and are thus considered important mediators of intercellular communication [6].

Depending on the size and the mode of formation, it is possible to distinguish small EVs or sEVs, including exosomes, and large EVs or lEVs. Exosomes measuring 30–150 nm in size are derived from MVEs and are released through a process of fusion with the cell membrane [7]. In contrast to lEVs, which can be as large as 1000 nm, are formed by the outward budding of the cellular membrane. They are heterogeneous structures containing the contents of the cell from which they were derived; due to the selective loading of molecules, such as miRNAs, they have proved useful in biomarker studies, particularly in the context of haematological malignancies, including AML [3,8]. MiRNAs control gene expression by regulating translation of target mRNAs, and their levels are responsive to the cellular context [9]; thus, they are potential diagnostic and therapeutic markers.

As stated above, both EVs, especially sEVs, have been found to communicate with the cells within the TME, such as hematopoietic and mesenchymal stem cells, MDSCs, and endothelial cells in AML [10,11]. They enhance leukemic cell survival, proliferation, and protect these cells from undergoing apoptosis. Tumor-derived EVs are also involved in angiogenesis, immune evasion, and disease progression by transferring oncogenic mutations and changing the TME [12,13]. For instance, Leukemic EVs have been shown to modulate angiogenesis through the delivery of proangiogenic signals. Also, the delivery of specific miRNAs by EVs can modulate the behaviour of both leukemic and normal cells and contribute to the progression of leukemia [14].

Due to their involvement in AML development, EVs have been considered for use in diagnostics and for drug delivery [15]. Their cargo represents the phenotype of the producing cell, and thus, it is possible to discern disease-specific patterns that could facilitate the progress of both diagnostic and therapeutic approaches [16]. Therefore, the concept of EVs opens new horizons in knowing the biology of AML and enhancing the quality of life of the patients (Table 1).

While substantial progress has been made in characterizing EVs in AML, the field remains largely descriptive and fragmented. Key molecular pathways mediated by EV cargo—particularly miRNA-driven regulation of apoptosis, immune evasion, metabolic adaptation, and therapy resistance—are often studied in isolation, with limited integration across disease stages or treatment contexts. Contradictory findings regarding the prognostic significance of specific EV-associated miRNAs (e.g., miR-126, miR-155) highlight the influence of AML heterogeneity, EV cellular origin, and methodological variability. Moreover, critical knowledge gaps persist concerning causality versus correlation, functional specificity of EV subtypes, and the dynamic remodeling of EV cargo during therapy. Emerging models suggest that EVs act not merely as passive biomarkers but as active regulators of leukemic ecosystems, necessitating deeper mechanistic studies and standardized analytical frameworks to translate EV biology into clinically actionable tools.

Table 1: Roles and therapeutic potential of extracellular vesicles in Acute Myeloid Leukemia (AML).

Category	Description	Significance in AML	References
Acute Myeloid Leukemia (AML)	Aggressive cancer affecting the BM and PB; leads to anemia, infection, and hemorrhage.	High relapse rate and resistance to treatments highlight the need for novel diagnostic and therapeutic approaches.	[17]
Current Treatments	Includes chemotherapy and stem cell transplantation	Effective in inducing remission, but limited by relapse and resistance	[18]
Extracellular vesicles (EVs)	Membranous particles containing lipids, nucleic acids, and proteins, secreted by most cells	Facilitates intercellular and intracellular communication; critical in AML progression.	[6]
Types of EVs	- **Small EVs (sEVs):** 30–150 nm, includes exosomes, from MVEs	sEVs, especially exosomes, transfer miRNAs and modulate cell signaling in AML	[19]
	- **Large EVs (lEVs):** Up to 1000 nm, formed by outward budding of the cell membrane	lEVs carry cellular contents and may be useful in biomarker studies	[20]
Role of miRNAs in EVs	miRNAs regulate gene expression by targeting mRNA and influence translation	Potential diagnostic and therapeutic markers in AML	[21]
EVs in Tumor Microenvironment	EVs interact with cells in the TME, including hematopoietic, mesenchymal stem cells, MDSCs, and endothelial cells.	Enhance leukemia cell survival, proliferation, immune evasion, angiogenesis, and disease progression.	[22]
Therapeutic Potential	EVs' cargo reflects the phenotype of the producing cell, allowing disease-specific pattern recognition.	Useful for AML diagnostics, prognostics, and drug delivery; opens new avenues for understanding AML biology and treatment.	[23]

Note: BM, Bone marrow; PB, Peripheral Blood; MVEs, Multivesicular Endosomes; TME, Tumor Microenvironment; MDSCs, Myeloid-Derived Suppressor Cells; AML, Acute Myeloid Leukaemia.

2 Exosomal Antigens in AML

Exosomes derived from AML have various types of specific tumor antigens and other biomolecules that are part of the characteristics of the disease and its interaction with the host immune system [24]. Some of the most important protein antigens found on the surface of AML-derived exosomes include Cluster of Differentiation 33 (CD33), CD34, and CD117, and exosomes isolated in AML patients have been found to have a much higher total protein content than those isolated in healthy patients [25]. In addition to these surface markers, AML exosomes also carry leukemia-associated antigens and immunosuppressive ligands, which include Transforming Growth Factor beta (TGF-β) and Interleukin-10 (IL-10) [26,27]. AML exosomes also carry an expanded molecular cargo beyond proteins to a wide variety of nucleic acids, including messenger RNAs (mRNAs), many microRNAs (miRNAs) such as miR-10b, miR-125b, miR-155, miR-21, miR-4532, miR-548ac, and miR-34c-5p, long non-coding RNAs (lncRNAs), and even double-stranded

DNA [28,29]. All these exosomal components have complex roles in the pathogenesis of AML: they are strong immunosuppressants, allowing the leukemia cells to avoid the host immune system by interfering with the activity of different immune cells, such as induction of apoptosis in activated $CD8^+$ T cells and expansion and activation of regulatory T (Treg) cells, partially via delivery of TGF-beta and IL-10 [26,30]. Moreover, AML exosomes play a role in leukemogenesis and cell survival by modifying the bone marrow microenvironment to support leukemic cell expansion, and suppress normal haematopoiesis, and by providing leukemic cells with growth, migration, and apoptosis resistance factors via transfer of oncogenic miRNAs and anti-apoptotic proteins [31,32]. These exosomal antigens and their full molecular cargo, presence in many body fluids, and the relative ease of isolation, could serve as attractive biomarkers of AML diagnosis, disease monitoring, and prognosis, applicable to the detection of leukemia relapse and drug resistance status [33]. Moreover, exosomes loaded with tumor-associated antigens have a significant application in AML therapy, including cell-free tumor therapy of minimal residual disease and as part of exosomal immune vaccines, including those based on TGF-beta 1-silenced leukemia cells or exosomes used to pulse DCs to induce tumor-specific cytotoxic T lymphocytes [31].

EVs released during chemotherapy or cellular stress have the potential to contain pro-apoptotic or immunostimulatory cargo, suggesting stage- and treatment-specific effects [34]. Likewise, EV-related miRNAs like miR-126 and miR-155 are associated with poor prognosis and resistance, but their functional effect differs across AML subtypes, EV cellular origins, and in experimental models, showing the shortcomings of mostly correlative research [35]. AML-derived exosomes are selective in antigenic and molecular repertoire of leukemic immunophenotype and genetics. Surface markers including CD33, CD34 and CD117 reflect blast and leukemic stem/progenitor cells and can affect the response of targeted treatments, especially targeting CD33 [36]. Moreover, exosomes also carry leukemia-associated antigens (e.g., WT1, PRAME, survivin, NPM1-derived peptides) and oncogenic nucleic acids, such as FLT3-ITD and mutant NPM1 transcripts, which makes them useful in immune surveillance and non-invasive estimation of disease burden [37,38]. The immune evasion rather than effective antitumor immunity is more often caused by exosomal HLA class I and II that co-express immunosuppressive ligands, including PD-L1 or TGF-b, although their regulation can have therapeutic potential [39].

3 Role of Extracellular Vesicles in Acute Myeloid Leukemia Diagnosis

The role of exosomes and other extracellular vesicles in the diagnosis of different cancers, including AML, has been determined [40,41]. In AML, the use of EVs as diagnostic biomarkers is beginning to receive attention because of their ability to mirror the molecular characteristics of leukemic cells, and their ease of isolation from body fluids; in addition, they are involved in cell signalling that supports leukemic cell proliferation (Table 2) [42].

Table 2: Main components and clinical applications of EVs in AML diagnosis.

Component	Content	Clinical Value	References
miRNAs	miR-155, miR-150, miR-126	Disease progression and chemotherapy resistance markers	[43]
Surface Proteins	CD9, CD63, CD81 (tetraspanins)	Identification of EV origin and characterization	[44]
Leukemia Markers	CD33, CD34, CD117	Classification of AML subtypes	[45]
Liquid Biopsy	Blood and other body fluids	Non-invasive monitoring and frequent sampling	[46]

Table 2: *Cont.*

Component	Content	Clinical Value	References
Molecular Cargo	Oncogenic mutations, mRNAs	Early disease detection and MRD monitoring	[47]
Prognostic Markers	miRNA expression levels	Prediction of survival rates and treatment outcomes	[48]
Technical Methods	Ultracentrifugation, chromatography, immunoaffinity	Isolation and characterization of EVs	[49]
Advanced Analysis	NTA, flow cytometry, NGS	Enhanced sensitivity in EV characterization	[50]

Note: miR, microRNA; CD, Cluster of Differentiation; NTA, Nanoparticle Tracking Analysis; NGS, Next-Generation Sequencing; EV, Extracellular Vesicle; MRD, Minimal Residual Disease; AML, Acute Myeloid Leukemia.

3.1 Composition of EVs As Biomarkers

EVs released to the extracellular space by AML cells contain a load of molecules that can be seen as surrogates of the malignancy itself, such as specific proteins, microRNAs, and mRNAs, as well as oncogenic mutations and, therefore, can be viewed as promising candidates for non-invasive biomarkers [51]. Another characteristic parameter of AML-derived EVs is their content, namely, specific miRNAs that are overexpressed in Leukemia [52]. These miRNAs have been known to be overexpressed in AML and are usually linked with disease progression, chemotherapeutic resistance, and unfavourable prognosis, and include miR-155, miR-150, and miR-126 [53]. In a diagnostic context, identification of the miRNA profile of EVs may offer a clue to the existence of AML, its progression, and the effect of therapy.

Besides miRNAs, AML-derived EVs also contain proteins that make them suitable biomarkers as well. For example, AML exosomes may express membrane proteins including tetraspanins (CD9, CD63, CD81), integrins, and leukemia-associated surface markers like CD33, CD34, and CD117 [54,55]. These markers are useful in the identification of normal and leukemic cells, and in the classification of particular subtypes of AML. Another aspect of the diagnostic potential of the protein cargo is that it identifies the cellular source of the EVs, as well as the functional state of the AML cells.

3.2 EVs in Liquid Biopsy

Another advantage of using EVs for diagnosing AML is their applicability to liquid biopsy, which is the test for cancer biomarkers in blood and other fluids. Conventional AML diagnosis involves the use of bone marrow biopsies, which are painful and may not be possible in some patients [56]. Invasive procedures are mitigated in this by the fact that clinicians can analyze the molecular profile of AML directly from blood or any other body fluid using EVs [57].

The isolation and profiling of EVs in liquid biopsy can provide a dynamic picture of the status of AML [58]. This dynamic and non-invasive modality of AML can be especially useful for early diagnosis, response assessment to therapy, and identification of minimal residual disease (MRD) after treatment [59]. In addition, since EVs are long-circulating in the blood and can shield their content from degradation [60], it is possible to collect diagnostic material from the same patient at different time points.

3.3 Early Detection and Monitoring of Disease Progression

Understanding the molecular signals of AML is crucial for better early detection, and EVs have been shown to be a good candidate in this regard. Since AML-derived EVs contain molecular markers such as

leukemia-associated mutations, specific miRNA profiles, and proteins, the molecular content of the EVs can be identified before clinical signs of AML develop or before changes in other clinical markers become apparent [61]. Researchers have noticed that certain specific biochemical markers can be associated with AML, and by using them, clinicians may be able to diagnose the onset of leukemia at an even earlier stage than by more conventional means, which could obviously be a great potential advantage [62]. The cargo of EVs changes with progression of the disease, tumor microenvironment, genetic changes, and response to treatment [63]. For instance, during chemotherapy, the expression of miRNA and protein in EVs may change to express leukemic cell death or drug resistance [64]. The quantitative and qualitative analysis of EVs in patients' blood can give real-time information about the response to treatment and the persistence of leukemic cells, allowing changes in therapeutic approaches.

3.4 Minimal Residual Disease (MRD) Detection

Identifying MRD is significant to define responsiveness to treatment and the likelihood of relapse [65]. The standard techniques for MRD detection include flow cytometry and PCR, which have certain drawbacks in terms of sensitivity and are unable to detect all residual leukemic cells [66]. A new strategy to achieve MRD detection can be brought about by EVs because they contain molecular markers such as oncogenic mutations, miRNAs, and specific proteins in leukemic cells [67]. The detection of the leukemia-associated EVs in the blood after treatment is suggestive of the persistence of the disease, though the standard techniques may not be able to pick them up [68].

3.5 Prognostic Value of EVs

However, EVs are not only informative of diagnosis but also possess strong prognostic capabilities in AML [69]. The molecular content of EVs can help to determine how malignant the disease is, whether the patient is likely to respond to treatment or not, and their life expectancy [70]. Research has presented evidence that certain miRNA in the EVs correlates with chemotherapy resistance, disease progression, and relapse in AML patients [71,72]. For instance, increased miR-155 expression in AML-derived EVs predicted lower survival rates and poor outcomes [73,74]. Likewise, high levels of exosomal miR-126 are related to higher levels of angiogenesis and disease progression [75].

When the content of EVs is analyzed, clinicians can categorize patients according to their risk of relapse or treatment failure and thus provide appropriate targeted therapies. For example, patients with high-risk EV profiles should be given stem cell transplantation, while those with low-risk EV profiles should be given less intensive treatment [76,77]. The possibility of evaluating prognosis by means of EV analysis contributes to the enhancement of treatment strategies and patient outcomes.

3.6 Technological Advances in EV Isolation and Characterization

Application of EVs as diagnostics in AML has been enhanced by developments in the isolation/characterization of EVs. Methods like ultracentrifugation, size exclusion chromatography, and immunoaffinity capture have enhanced the purity of the populations of EVs isolated from body fluids, and therefore, the molecular analysis of the contents of these vesicles is more precise [78]. Furthermore, the new technologies, including nanoparticle tracking analysis (NTA), flow cytometry, and next-generation sequencing (NGS), have improved the sensitivity and specificity of EV characterization to identify small amounts of leukemia-derived EVs in patient samples [79]. These technological innovations have rendered it feasible to profile the load of EVs with increased sensitivity, including isolation of specific miRNAs, proteins, and mutations that are related to AML diagnosis and prognosis [80]. With the advancement of the isolation and characterisation

methods of EVs, the application of EVs as diagnostic biomarkers for AML will continue to increase and be translated into the clinic.

4 Role of Extracellular Vesicles in Minimal Residual Disease Evaluation in AML

MRD is a small number of cancer cells that may remain in a patient's body after treatment, and which can cause relapse [81]. MRD assessment in AML is important for the evaluation of treatment response and to guide subsequent therapy (Table 3). Here, researchers found that certain mutations, transcripts, or proteins associated with AML are also detectable and can be utilized as biomarkers of minimal residual disease [82]. For example, mRNA cargo, including a specific molecular signature associated with the tumour, is packaged inside exosomes originating from leukemic cells, for instance, FLT3 or NPM1 [83]. The identification of these biomarkers in circulating EVs offers a blood-based strategy for the identification of MRD. This is especially beneficial over other bone marrow biopsies that are invasive and may not capture the entire leukemic population. A comprehensive overview of key aspects and components in EV-based MRD detection for AML (Fig. 1).

Table 3: Role of extracellular vesicles in assessing minimal residual disease in Acute Myeloid Leukemia.

Aspect	Details	Significance	Challenges	References
Definition of MRD	Small amounts of cancer cells remaining post-treatment may lead to relapse.	Critical for understanding the risk of recurrence.	Difficult to detect with conventional methods.	[84]
Importance of MRD Assessment	Evaluates treatment response and informs future therapeutic strategies.	Helps tailor individualized treatment plans for AML patients.	Requires sensitive and specific detection methods.	[85]
Role of Extracellular Vesicles	EVs, especially exosomes, carry molecular information from parent cells relevant to MRD assessment.	Provides a non-invasive method for monitoring disease status.	Standardization in EV isolation techniques is needed.	[86]
Biomarkers in EVs	Detectable mutations, transcripts, or proteins related to AML (e.g., FLT3, NPM1) found in EVs.	Can serve as reliable indicators of residual disease presence.	Variability in biomarker expression across patients.	[87]
Advantages of EVs	Blood-based MRD identification is less invasive than bone marrow biopsies, potentially capturing the full leukemic population.	Enhances patient comfort and accessibility to monitoring.	Limited availability of standard protocols for analysis.	[68]
Molecular Methods for EV Cargo	Advanced techniques like NGS and RNA sequencing can identify cargo in EVs.	Enables comprehensive profiling of genetic content in EVs.	High technical requirements and costs of molecular assays.	[88]
Clinical Insights	Exosome profiling reveals kinetics of residual disease; re-emergence of mutations may indicate leukemic cell presence.	Guides decisions on therapy intensification or modification.	Interpretation of results may vary among clinicians.	[89]

Table 3: *Cont.*

Aspect	Details	Significance	Challenges	References
Risk Assessment	Persistent molecular markers in EVs may classify patients as high risk for relapse; MRD-negative patients may have better outcomes.	Allows for tailored monitoring and preventive strategies.	Need for consensus on risk stratification criteria.	[90]
Future Directions	More studies are needed to validate EV-derived biomarkers across diverse patient populations and establish clinical relevance.	Essential for integrating EV analysis into routine clinical practice.	Overcoming regulatory and logistical hurdles for implementation.	[91]

Note: AML, Acute Myeloid Leukemia; MRD, Minimal Residual Disease; EVs, Extracellular Vesicles; NGS, Next-Generation Sequencing; RNA, Ribonucleic Acid; FLT3, Fms-like Tyrosine Kinase 3; NPM1, Nucleophosmin 1.

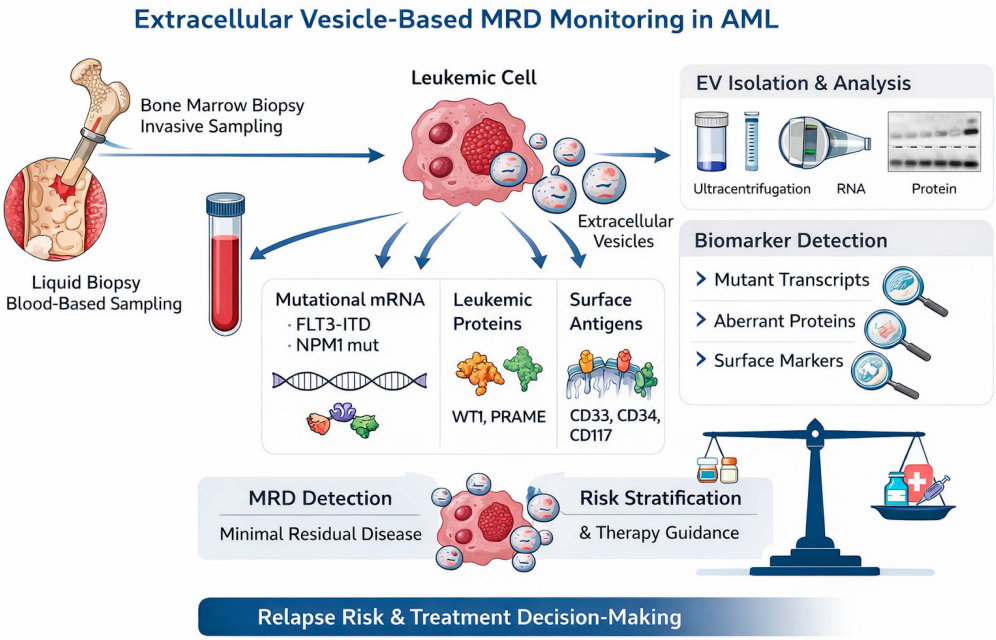

Figure 1: Conceptual Framework of Extracellular Vesicles in MRD Assessment. Leukemic cells release EVs into peripheral blood, from which they are isolated and analyzed for leukemia-associated transcripts and proteins. EV-derived biomarkers are incorporated into MRD evaluation to inform clinical decision-making. (This figure is original and was created using BioRender.com, version 2024, developed by BioRender Inc. (Toronto, Canada).

It has been shown that cargoes of EVs can be identified using more profound molecular methods, including next-generation sequencing and RNA sequencing [92]. Clinicians using exosome profiling of the genetic content in patients during and after treatment can get a glimpse of the kinetics of the residual disease [93].

Furthermore, EVs in MRD assessment can also improve the risk assessment of patients. Patients with persistent molecular markers in their EVs might be considered high risk for relapse, so that they can be monitored more closely and treated prophylactically [94]. On the other hand, patients who were MRD negative in their EVs may have a better prognosis [95], and this may determine their further management

and follow-up. However, while the promise of using EVs for MRD evaluation is significant, challenges remain. Standardization in the isolation and characterization of EVs is crucial to ensure that findings are reproducible and clinically applicable [96]. Additionally, further studies are necessary to validate the use of EV-derived biomarkers in diverse patient populations and to establish their clinical relevance in predicting relapse.

5 Role of Extracellular Vesicles in Bone Marrow Transplant Chimerism Evaluation in AML

BMT is one of the main anti-AML therapies, especially for patients after multi-agent chemotherapy and with a high risk of disease relapse [97]. One of the important components of BMT is so-called chimerism, which is the ratio of donor versus recipient hematopoietic cells in the patient's bone marrow [98]. The definitive determination of chimerism is critical for the overall assessment of transplantation outcomes and for the timely identification of possible relapse [99].

Recent data suggest that extracellular vesicles (EVs) could be used for the assessment of chimerism in BMT recipients. These nanosized vesicles, as exosomes, originated from both donor and recipient cells, can incorporate nucleic acids, proteins, and other biomolecules that can represent the state of the hematopoietic niche [100]. Studying the cargo of EVs isolated from the peripheral blood of transplant recipients allows the identification of the dynamics of chimerism and the relative proportion of donor and recipient cells.

The content of EVs can be studied by molecular methods, including quantitative polymerase chain reaction (qPCR), NGS, and mass spectrometry (MS) [101,102]. For instance, the EVs contain specific biomarkers that define the donor or recipient nature of the hematopoietic cells in the bone marrow [103]. If donor-specific markers are present in EVs and at the same time the level of recipient markers is low, it would mean that the engraftment process has occurred and the response to the transplant is positive [104,105].

Moreover, the evaluation of the levels of chimerism through the analysis of EV can give the possibility to assess the patient's response to the treatment and the risk of relapse in real-time [106]. If in an EV, the proportions of the recipient markers are observed to be rising, it can be understood that the original leukemic population is resurging and requires urgent treatment. This ability to determine the level of chimerism not only at distant time points but also intermittently helps clinicians to fine-tune the therapy strategy to reflect the changes in the disease process, thereby increasing the likelihood of a prolonged disease-free survival.

The application of EVs in chimerism assessment also has potential for non-invasive follow-up. The conventional approaches involve procedures that are painful to the patient, for instance, bone marrow punctures (Table 4). However, evaluation of circulating EVs is less invasive, which allows performing repeated tests with slight discomfort to the patient.

Table 4: Role of extracellular vesicles in assessing chimerism in Bone Marrow Transplantation.

Aspect	Details	Significance	Challenges	References
Definition of Chimerism	Ratio of donor versus recipient hematopoietic cells in the patient's bone marrow.	Critical for assessing transplantation outcomes and identifying relapse.	Difficult to measure accurately with conventional methods.	[99]
Role of Extracellular Vesicles	EVs, including exosomes, are produced by both donor and recipient cells and can reflect the hematopoietic niche.	Provides insight into the dynamics of chimerism post-transplant.	Requires careful analysis of EV content for accuracy.	[107]

Table 4: *Cont.*

Aspect	Details	Significance	Challenges	References
Molecular Methods for EV Cargo	Analyzed using qPCR, NGS, and MS to study the content of EVs.	Enables identification of specific biomarkers indicating donor/recipient nature.	Technical complexity and cost of methods.	[101]
Indicators of Engraftment	Presence of donor-specific markers with low recipient markers indicates successful engraftment.	Helps confirm a positive response to the transplant.	Variability in biomarker expression across individuals.	[108]
Real-Time Assessment	Analysis of EVs allows for real-time monitoring of chimerism and potential relapse.	Facilitates timely intervention if leukemic cells are re-emerging.	Requires ongoing monitoring and data interpretation.	[109]
Noninvasive Follow-Up	Circulating EVs allow for less painful monitoring compared to traditional methods like bone marrow biopsies.	Improves patient comfort and enables frequent testing.	Still requires standardization in EV isolation protocols.	[110]
Future Directions	More research is needed to establish the clinical relevance of chimerism markers in diverse patient populations and protocols.	Essential for the broader clinical application of EV analysis.	Need to define standard protocols for EV characterization.	[111]

Note: EVs, Extracellular Vesicles; qPCR, Quantitative Polymerase Chain Reaction; NGS, Next-Generation Sequencing; MS, Mass Spectrometry.

However, some issues have to be considered: Specificity and reproducibility of the data depend on the standardization of the procedure for the isolation and characterization of EVs [49]. However, more work is required to define the clinical relevance of the chimerism markers detected within EVs in other patients and treatment protocols.

6 Role of Extracellular Vesicles in Multidrug Resistance in AML

MDR is a major problem in Acute Myeloid Leukemia (AML) patients and results in treatment failure and poor prognosis [112]. MDR can occur through a number of processes, such as the action of efflux pumps, changes in the receptor site, and changes in apoptotic pathways [113]. Recent studies have identified that extracellular vesicles (EVs) are critical for AML MDR since they allow the transfer of resistance-related molecules between different cells [61,71,114,115] (Table 5). One of the most important ways through which EVs are involved in MDR is by delivering drug efflux transporters, including P-glycoprotein (P-gp) [113]. Since leukemic cells in the case of P-gp overexpression can release EVs containing this protein, the latter can be internalized in the neighbouring sensitive cells [116]. This transfer of P-gp allows the recipient cells to pump out chemotherapeutic agents, thereby reducing their concentration within the cell and contributing to resistance [117]. This phenomenon thereby establishes a niche within which drug-resistant cells can practically reign, while at the same time, sensitive cells lose their ability to respond to treatment [118,119]. EVs may harbor miRNAs that negatively regulate apoptosis-promoting signals or positively regulate anti-apoptosis signals in the target cells [119]. This exchange of resistance-associated cargo not only

supports cell viability in the presence of chemotherapeutic compounds but also the general leukemic population's resistance.

The use of EVs in regulating MDR has serious implications for the clinical management of AML. Once a specific EV cargo related to resistance has been defined, it becomes possible to design therapies that will not be affected by these mechanisms [120]. For instance, new therapies that would prevent cells from releasing EVs or prevent sensitive cells from absorbing EVs would increase the effectiveness of traditional chemotherapeutic drugs [121].

Besides, EVs can also potentially be used for the early identification of patients who are likely to develop resistance and for the assessment of treatment response. The identification of the molecular changes that underlie resistance can be achieved through the analysis of the EVs in patients during the course of treatment, with a view to modifying the treatment regimens [122]. This could enhance the therapeutic benefit by pinpointing other therapies or the combined regimen that is effective against a resistant leukemic population.

However, there are several limitations of using EVs in unraveling and eradicating MDR in AML patients. The large variety of EVs and their content makes the interpretation of the results more challenging [122,130]. This calls for the standardization of methods used for the isolation and characterization of EVs in order to have comparable results across different research works. Furthermore, expanded clinical trials are needed to confirm the use of EVs as prognostic markers for drug resistance in AML. Further studies should also aim to identify the exact molecular mechanisms through which EVs mediate resistance and determine the potential treatment strategies targeting EV-associated pathways.

Table 5: Role of extracellular vesicles in multidrug resistance in Acute Myeloid Leukemia.

Aspect	Details	Significance	Challenges	References
Definition of MDR	MDR is a major issue in AML that leads to treatment failure and poor prognosis.	Impacts patient outcomes significantly by limiting the effectiveness of therapies.	Complex mechanisms involved; multifactorial nature of resistance.	[123]
Role of Extracellular Vesicles	EVs facilitate the transfer of resistance-related molecules between cells, playing a critical role in MDR.	Enhances the ability of resistant cells to influence neighboring sensitive cells.	Diversity of EVs complicates the understanding of their roles.	[116]
Efflux Transporters	EVs can deliver drug efflux transporters (e.g., P-glycoprotein) from resistant to sensitive cells.	Allows sensitive cells to expel chemotherapeutic agents, promoting resistance.	Determining the specific mechanisms of transporter transfer.	[124]
miRNAs and Apoptotic Proteins	EVs can transfer miRNAs and proteins that modulate apoptotic pathways, supporting cell viability.	Helps maintain leukemic cell survival in the presence of chemotherapy.	Identifying specific miRNAs and their roles in resistance.	[125]
Clinical Implications	Understanding EV cargo can lead to therapies that bypass resistance mechanisms or inhibit EV release/absorption.	Potentially increases the effectiveness of traditional therapies.	Requires extensive research to translate findings into practice.	[126]

Table 5: *Cont.*

Aspect	Details	Significance	Challenges	References
Early Identification of Resistance	Analyzing EVs may help identify patients likely to develop resistance and assess treatment responses.	Enables timely modifications to treatment regimens, enhancing therapeutic efficacy.	Need for robust clinical validation and standardized protocols.	[127]
Limitations	Varied EV content complicates interpretation; standardization of isolation and characterization methods is needed.	Comparable results across studies are essential for progress.	Further clinical trials are needed to confirm EVs as prognostic markers.	[128]
Future Directions	Research should focus on identifying molecular pathways through which EVs mediate resistance and treatment strategies.	Essential for developing targeted therapies that address EV-associated pathways.	Identifying effective strategies for targeting EVs in clinical settings.	[129]

Note: MDR, Multidrug Resistance; AML, Acute Myeloid Leukemia; EVs, Extracellular Vesicles; P-gp, P-glycoprotein; miRNAs, microRNAs.

7 Role of Extracellular Vesicles in Chemotherapy Response in AML

Chemotherapy is widely used for the treatment of AML; the standard approach includes intensive schedules aimed at the eradication of leukemic cells and achievement of remission [131,132]. However, similar to most malignancies, AML is a heterogeneous disease and has MRD that results in treatment failure and relapse [133]. It is important to establish the reasons why certain patients respond to chemotherapy, while others do not, so as to enhance the implementation of chemotherapy and improve the care of patients.

Extracellular vesicles (EVs) are becoming recognized as important protagonists in the interaction of AML cells with chemotherapy. These vesicles can help cells to communicate with each other and can also alter many biological signals, such as drug resistance and cell death [71]. The content of EVs is related to the physiological state of their source cells and may contain information about the mechanisms of treatment effects [134].

EVs can transfer molecules related to resistance from one cell to another, leading to a shift of phenotype of the neighbouring sensitive cells to a more resistant one. This makes it difficult to determine the response of the tumor to chemotherapy since the presence of a drug-resistant subpopulation affects the overall treatment response [135]. On the other hand, chemotherapy is capable of stimulating the release of apoptotic EVs with molecules that are relevant to cell death, thus enhancing the impact of treatment [136].

The analyses of EVs concerning chemotherapy response also open up prospects for biomarker creation. Evaluation of the molecular content of the collected EVs from patients with chemotherapy allows assessing the effectiveness of the treatment. For example, the concentration of certain miRNAs or proteins in the EVs could be related to the treatment response and can be utilized as biomarkers of therapeutic efficacy. Favourable patient response may entail a reduction in the levels of EVs that bear markers of resistance or an upregulation of EVs with pro-apoptotic properties [137].

Furthermore, the use of EVs for monitoring chemotherapy response offers a non-invasive approach that complements traditional methods. If the analysis of EVs reveals persistent markers of resistance, clinicians may choose to modify the treatment regimen or consider alternative therapies [110].

While the role of EVs in chemotherapy response is promising, several challenges remain. Standardization in EV isolation and characterization is essential for ensuring the reliability and reproducibility of findings [49,138]. Moreover, further research is needed to establish the clinical significance of EV-derived biomarkers across diverse patient populations and treatment regimens. Understanding the mechanisms by which EVs influence chemotherapy response will also require in-depth investigations into the molecular pathways involved.

8 Small EVs As Potential Therapeutic Tools

Small extracellular vesicles (sEVs) are a subpopulation of extracellular vesicles that have attracted increasing interest in recent years because of their specific characteristics and possible use in medicine [139,140]. In Acute Myeloid Leukemia (AML), sEVs are also becoming important not only as biomarkers but as potential therapeutic agents. These nanosized vesicles are involved in intercellular communication and can transport a variety of biomolecules, such as proteins, lipids, and nucleic acids that represent the physiological condition of their parent cells [141].

Another feature of sEVs that attracts much attention is that they can act as therapeutic carriers [142]. Scientists are investigating the ability of engineering sEVs to transport therapeutic cargo more efficiently to the target cells, increasing the effectiveness of current therapies and overcoming the challenges of drug delivery [143]. For example, sEVs can be loaded with antineoplastic drugs or RNA drugs, including siRNA or microRNA, to control gene expression in leukemic cells [144]. A key advantage of this targeted delivery system is that it increases the therapeutic index by decreasing side effects and the toxicity to normal cells.

In addition, due to the inherent property of sEVs to mediate intercellular communication, sEVs are potentially suitable for the development of immunotherapeutic strategies. When the payload of sEVs is altered to comprise immunogenic peptides or co-stimulation markers, the immunological reaction against leukemic cells is improved. This approach could potentially enhance the efficacy of existing immunotherapies, including checkpoint inhibitor or CAR T-cell therapies, through the use of sEVs' immune-modulatory properties [145].

Besides their application in AML treatment, sEVs are also suitable for biomarker-based assessment of disease progression and therapeutic outcomes [146]. The molecular content of sEVs can act as a rich source of information concerning the mechanisms of leukemogenesis and resistance to therapy. For instance, some miRNA or proteins in sEVs may be associated with the treatment outcome and, therefore, the efficiency of the treatment can be assessed in real-time [147]. It can help clinicians make better treatment plans for patient care, enhancing the overall results they get in patients.

However, there are still some issues to be considered with regard to the application of sEVs in AML treatment. Standardization of sEV isolation and characterization methods is critical for the purposes of comparison and confirmation of obtained data. Furthermore, the biological effects of sEVs on the recipient cells involve multiple signalling pathways that need to be better understood to enhance the therapeutic potential of sEVs [148]. Further work should be dedicated to understanding how exactly sEVs work and how to properly load and deliver the therapeutic payload. Exploring the use of sEVs in combination with conventional treatments might also improve patients' prognosis in AML. Overall, small EVs have a high potential for being used as therapeutic carriers in Acute Myeloid Leukemia. Given their ability to deliver therapeutic agents selectively and act as biomarkers for disease progression, sEVs are a novel solution to enhancing treatment methods. Further studies in this field are needed to optimize the usage of sEVs in AML treatment and improve the quality of life of patients.

9 Role of Exosomes in Tumor Progression and Survival in AML

About Acute Myeloid Leukemia (AML), exosomes have been considered for their ability to support the survival of tumors and advance disease [149,150]. Exosomes derived from AML cells can transfer pro-survival signals to neighbouring leukemic cells, promoting their survival. Thus, the transfer of such factors, exosomes establish a favorable stroma that supports tumor development and treatment evasion [83,151]. Among them, miR-125b is one of these transferred miRNAs that repress the expression and function of several pro-death proteins like BAK, Bmf, and P53 in leukemia cells. Furthermore, miR-125b not only inhibits the apoptosis of leukemia cells but also promotes the survival and proliferation of AML cells by stimulating cell cycle (Fig. 2) [152–154]. The latter mechanism of action enables leukemic cells to remain unimpaired by the effects of chemotherapy and hence leads to treatment failure.

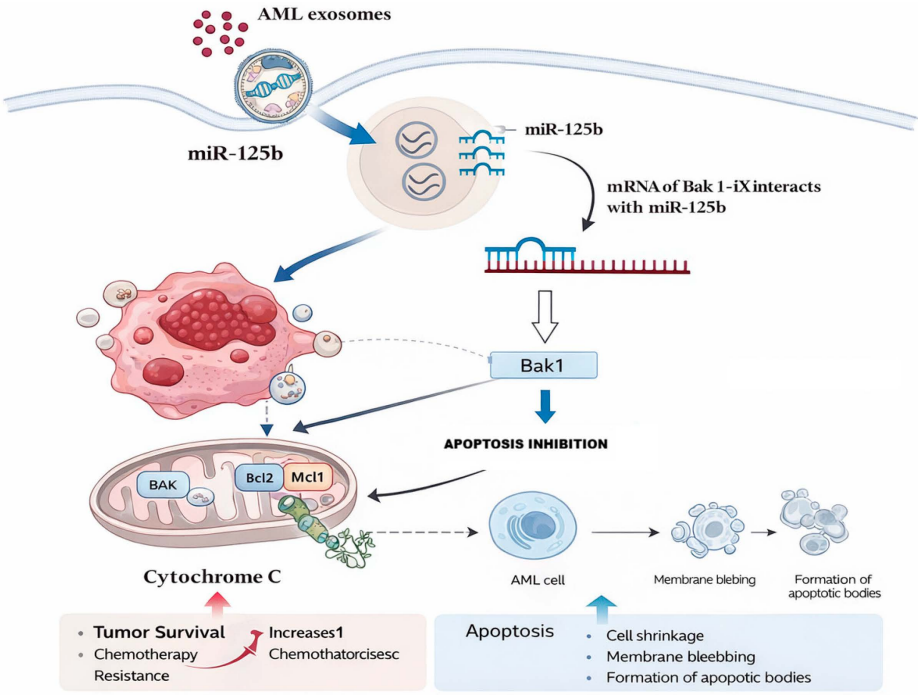

Figure 2: Exosomal miR-125b–mediated inhibition of apoptosis in Acute Myeloid Leukemia. AML-derived exosomes transfer miR-125b to leukemic cells, where it suppresses the pro-apoptotic protein Bak. Reduced Bak expression prevents mitochondrial outer membrane permeabilization, cytochrome c release, and caspase activation, promoting leukemic cell survival and chemoresistance. (This figure is original and was created using BioRender.com, version 2024, developed by BioRender Inc. (Toronto, Canada).

Leukemic cells can release exosomes that can prevent dendritic cells from developing into mature cells and initiate an appropriate immune response against tumor cells [155,156]. Furthermore, exosomes can modulate T cell activity by transferring immunosuppressive messages to suppress immune responses and support tumour persistence [157]. It also showed that exosomes can express signals that promote migratory and invasive capabilities and thereby assist in the spread of AML cells to distant organs. Exosomes may enhance tumor angiogenesis, which is required for tumor growth and metastasis [158]. In the clinical setting, they can be useful in biomarkers for monitoring the disease progress and or outcome. The molecular cargo of exosomes is derived from their parent cells, and the analysis of their content can help understand

disease progression and response to therapy. Specific mutations or transcripts could be detected in exosomes and can be used to identify the MRD for the prognosis of relapse and to guide the treatment [159].

The identification of the function of exosomes in tumor advancement may provide insight into new treatments. Approaches to suppress the release of exosomes or to prevent the uptake by target cells could improve the therapeutic outcome and bypass resistance [160]. In targeting exosomal pathways, new strategies may be identified to enhance treatment profiles in AML.

However, several factors that will need to be addressed in order to effectively target exosomes in AML are still alluded to. Heterogeneity of exosome origin and their content makes it challenging to conclude the research studies conducted in this field.

10 Technical and Methodological Barriers to Clinical Translation

The availability of standardized procedures in the isolation, characterization, and analysis of EV is another significant impediment to the clinical implementation of EV-based therapy in AML. Populations of heterogeneous vesicles, with contamination by lipoproteins, protein aggregates, and ribonucleoprotein complexes varying in content, are produced with the common techniques of differential ultracentrifugation, size-exclusion chromatography, precipitation-based kits, and immunoaffinity capture, especially in plasma-derived samples. Sample collection, storage, normalization, and analytical platform variability also undermine reproducibility and cross-study comparability, and question whether the reported EV biomarkers are indicative of technical artifacts and not disease-relevant biology.

The MISEV guidelines offer the necessary framework to enhance the rigor of the experiment, including complementary isolation and characterization methods, reporting them, and having the right controls. However, compliance is rather unstable, and EV identity, purity, and cellular background are often not properly verified. Poor separation of leukemia-induced EVs and normal hematopoietic/stromal cells, and patient-related confounders, including inflammation, infection, and treatment effects, remain to compromise the specificity of biomarkers.

11 Knowledge Gaps and Future Translational Opportunities

The unanswered questions are the actual leukemic input of circulating EV pools, the cause-effect role of EV cargo vs. passive release, and the biology of EV subtypes. The resolution of these problems will involve standardized approaches, multi-omics and functional studies, and longitudinal studies in patient cohorts of excellent character.

Translationalally, EV-based assays need to be assessed in large, prospective clinical trials in combination with other well-known diagnostic techniques, including flow cytometry and molecular minimal residual disease testing. EV profiling will not be able to substitute current tools, but could be used to give complementary information because of the dynamic and therapy-based changes in leukemic biology. Engineered EVs are a promising yet experimental approach to targeted delivery of drugs or nucleic acids therapeutically utilizing their biocompatibility and inherent targeting capabilities. Addressing the issues of scalability, quality control, and regulatory approval will be crucial to transform EV-based technologies into research tools into the clinically actionable elements of AML management.

12 Conclusion

Extracellular vesicles (EVs), especially exosomes, have become a key mediator of AML biology, connecting leukemic signalling, immune modulation, and resistance to therapy [161]. Their antigenic and

molecular cargo, such as CD33, CD34, CD117, and immunosuppressive factors, indicate disease conditions and lead to remodeling of the microenvironment and persistence of the leukemia.

EVs have distinctly translational capabilities because they are a stable, minimally invasive biomarker type of disease monitoring, minimal residual disease assessment, and early relapse prediction, and may be used alongside the established modalities of flow cytometry and next-generation sequencing. The development of EVs also makes them promising therapeutic delivery vehicles and immunomodulatory agents.

Nevertheless, clinical adoption is still impaired by the heterogeneity of methods used, the lack of standardization, and the absence of massive validation. Standardized protocols, future clinical studies, and incorporation into already existing diagnostic models will be necessary to address these issues to unlock the clinical potential of EV-based methods in AML.

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Abbreviations

EVs	extracellular vesicles
AML	Acute Myeloid Leukemia
BM	bone marrow
PB	peripheral blood
TME	tumor microenvironment
MRD	minimal residual disease
MDR	multidrug resistance
NGS	next-generation sequencing
BMT	bone marrow transplantation
MSC	mesenchymal stem cell

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