Exosomes Derived from Acute Myeloid Leukaemia (AML) have a Key Role in the Development and Survival of Tumors

Kyle Mary*, Chase Lisa

Editorial office, European Journal of Clinical Oncology, India

Corresponding Author*

Kyle Mary

Editorial office,

European Journal of Clinical Oncology, India

E-mail: oncology@scholarlymed.com

Received date: 04 -May, 2022, Manuscript No: ejco-22-75450; **Editor assigned:** 06-May-2022, PreQC No ejco-22-75450 (PQ); **Reviewed:** 08-May-2022, QC No. ejco-22-75450(Q); **Revised Date**: 14-May-2022, Manuscript No: ejco-22-75450 (R); **Published date:** 20-May-2022, doi: 10.35248/clinical-oncology. 4(3).34-35

Abstract

Acute Myeloid Leukemia (AML) is a quickly aggressive hematopoietic disorder that progress due to the accumulation and clonal expansion of immature myeloid cells. Despite the latest developments in AML treatment, repeated relapses and drug resistance remain one of the major challenges in treatment of leukemia. Currently, it is well known that the components of the tumor microenvironment such as cellular and non-cellular elements play a critical function in treatment failures of AML; also they are most common cause of complications including suppression of hematopoiesis. Exosomes are membrane-bound Extracellular Vesicles (EVs) that transfer signaling molecules and have attracted a large amount of attention due to their important role in inter-cellular communication in health and disease. Exosomes transport their diverse payload of chemicals, including miRNAs, growth factors, and cytokines, to leukaemia cells, aiding in their survival and chemoresistance. Bone marrow mesenchymal stem cells (BMSCs) and AML cells themselves are the principal exosome producers that primarily contribute to the pathogenesis of AML. Numerous target cells, including hematopoietic stem cells and Natural Killer (NK) cells, are impacted by the exosomes that these cells release, causing leukaemia to proliferate and grow. In the current work, a thorough review of the literature has been conducted to emphasise the importance of exosomes from AML in the progression of acute myeloid leukaemia and to briefly address the biology of exosomes.

Keywords: Acute myeloblastic leukemia • Extracellular vesicles • Exosomes • MiRNAs • Leukemia progression • Cancer

Introduction

Acute Myeloid Leukaemia (AML) is a group of blood and bone marrow cancers distinguished by inadequate myeloid cell maturation. At the Colony-Forming Unit (CFU) or later stages of differentiation, clonal over-proliferation of an aberrant, committed stem cell causes this malignant condition, which causes an accumulation of blasts, or non-functional myeloblasts, to form. Although myeloblasts frequently swiftly accumulate in the blood, they frequently pile up in the BM. Additionally, the immature cell may move to various organs such as the liver, spleen, lymph nodes, and central nervous system [1-2].

Imaging studies, biopsy, cytochemistry, and immunophenotyping are used to confirm the diagnosis of AML. Gene mutations, chromosome deletions, and translocations account for the majority of the clinically discernible disease in AML.

The investigations have demonstrated that the BM Microenvironment (BMM) is crucial in the pathogenesis of AML and the development of chemotherapeutic resistance. Exosomes, also known as Intraluminal Vesicles (ILVs), are a subtype of Extracellular Vesicles (EVs) that are membrane-bound and released by different cell types. They have been found in serum, plasma, urine, semen, saliva, bronchial fluid, cerebral spinal fluid, breast milk, amniotic fluid, synovial fluid, tears, lymph, bile, and gastric acid. A particular collection of preassembled payloads packaged into the exosomes may cause biological alterations in recipient cells depending on their original cells. Exosomes carry a variety of biologically significant cargoes. For example, the exosome populations generated by multiple myeloma cells exhibit unique microRNA (miRNA) expression profiles, such as miR-15a [3].

Exosomes regulate cell-cell communication, which is involved in many pathological and physiological processes, including those involved in cancer and other malignant disorders.

We will talk about the exosome's biosynthesis, composition, and significance in the aetiology and growth of AML in this review.

When examining the loss of transferrin through the development of reticulocytes in blood in the 1980s, researchers Pan, Stahl, and Johnstone represented an essential way of intercellular communication for the first time. EVs are lipid-bilayer-encapsulated particles that have been recognised as an essential intercellular communication mediator. Exosomes and microvesicles are the two primary types of EV in traditional biology (MVs). Exosomes are divided into two different subtypes of Extracellular Vesicles (EVs) based on their size, with MVs typically being larger than exosomes (diameter: 30 nm -150 nm) (100 nm –1000 nm in diameter). Exosomes and MVs have different biogenesis mechanisms, too. In physiological circumstances, notably during cell development, cells release MVs. These EVs are produced by the plasma membrane directly budding (PM).

Calpain is activated by an increase in intracellular cytosolic calcium, which mediates this action. By cleaving the actin protein network, this leads to the restoration of the cytoskeleton and, eventually, to budding.

Exosomes have unique biogenesis processes. The internal budding of the PM during the initial stage of exosome production results in the formation of an early endosome, which later undergoes a number of alterations to become a late endosome. The pinching off of the late endosomal membrane to create membrane-enclosed vesicles is referred to as ILVs in the following, and the late endosome is referred to as Multivesicular Bodies (MVBs) in the following. In the following phase, MVBs may combine with lysosomes to transfer ILV contents for breakdown or with PM to release ILVs as exosomes into the extracellular environment [4].

According to the research, the Endosomal Sorting Complex Required for Transport (ESCRT) machinery is either required or not required for the synthesis of exosomes. ESCRT-0 recognises the ubiquitinated contents and groups them into the endosomal membrane using a variety of components that make up the ESCRT machinery. To create ILVs, the ESCRT-I and ESCRT-II complexes stimulate the inward budding process. But the ESCRT-III stops this process by forcing the release of fresh ILVs. Ceramides, ADP ribosylation factor 6, sphingosine-1-phosphate, sphingolipids, heat-shock proteins, and the tetraspanin family are other ESCRT-independent processes that are important in the synthesis of exosomes.

Exosomes are first ingested by the target cell, and then their contents are released. It is unclear whether immune and non-immune cells must absorb exosomes in order for them to activate signalling. For instance, in order to start cellular signalling, the receiving cell needs to absorb RNA species. Contrarily, juxtacrine or soluble FasL and TRAIL signalling is related with location and transient adhesion and elicits cellular responses. The formation of clathrin-coated vesicles during clathrin-mediated endocytosis allows for the regulated insertion and internalisation of transmembrane content and ligands.

A growing body of research has shown that a variety of cell types, including epithelial, neuronal, cardiomyocyte, macrophage, hepatocyte, and ovarian and colon cancer cells, can internalise exosomes in this way. Transferrin receptors, which are crucial cargos for clathrin-mediated endocytosis and encourage exosome uptake, have been shown to be overexpressed in tumour cells. Phagocytosis, an actin-mediated mechanism, has been proposed as a different method of exosome internalisation. It requires specific opsonin, scavenger, and toll-like receptor expression [5].

According to the research, professional phagocytic cells, like macrophages and monocytes, are more effective than non-professional phagocytes at internalising exosomes produced from leukaemia.

Exosomes can also interact directly with recipient cells to affect them. They can interact with receptors to cause downstream signalling cascades by binding to recipient cells' membranes in extracellular space. Exosomes produced by dendritic cells can activate T lymphocytes via the MHC complex and can bind to Toll-like receptor ligands on bacterial surfaces to activate cellular signalling. Human umbilical cord blood exosomes containing *MHC-I, MHC-II, CD34, and CD80* promote T cell development and exert anticancer activity.

These nano vesicles can also combine with the PM and secrete their contents right into the recipient cells' cytoplasm. Studies on cell membrane fusion suggest that the Rab family and SNARE complex likely aid in this fusion. Exosomes also contain other structures that help the membrane contact, bind, and fuse with the destination cell, such as integrins, adhesion molecules, and micro-domains called lipid rafts.

Exosomes' role in the aetiology of AML is thoroughly studied. Exosomes play a key role in the progression of leukaemia by transporting essential oncogenic RNAs into hematopoietic stem cells, altering their characteristics and promoting the formation of leukemic cells. According to Fang et al., patients with AML had higher serum levels of exosomes expressing *miRNA-10b* compared to controls. The significant roles of this carrying structure in AML were suggested by the high levels of exosomes containing miR-10b in AML patients. By inhibiting granulocytic/monocytic differentiation in hematopoietic stem cells and boosting the proliferative capacity of immature myeloid cells, miR-10b plays a crucial role in the development of AML [6].

However, the rising levels of miR-10b in AML suggested that the gene may serve as a potential biomarker for the diagnosis of the disease. Another miRNA that is expressed in exosomes generated from AML is miR-4532. This miRNA increased the expression of DKK1 and decreased the expression of CFU in CD34+ hematopoietic stem cells. MiR-4532-containing exosomes produced by AML cells inhibited CFU by concentrating on LDOC1. According to a study by Lee et al., LDOC1 is crucial for the negative control of the STAT3 signalling pathway, therefore when it is reduced, JAK2 and STAT-3 activation are elevated.

One of the crucial criteria that could ensure the survival of leukemic cells in the BM is neovascularization. Exosomes have been demonstrated to be essential for angiogenesis. Exosomes from leukaemia induce the formation of tubular structures resembling blood vessels in HUVECs by transmitting miRNAs. By demonstrating that VEGFR mRNA was transported into the Endothelial Cells (ECs) and then translated into the proteins to promote VEGF signalling in HUVECs, Wang et al. showed that AML exosomes may contribute to heightened angiogenesis in leukaemia. Through the transmission of angiogenic factors/proteins and miRNAs, exosomes modify the characteristics of HUVECs and promote angiogenesis [7].

Conclusion

Exosomes are one type of extracellular vesicle that are released by a variety of cells and contain a variety of bioactive substances, such as proteins, lipids, nucleic acids, and metabolites. Exosomes from bodily fluids have been isolated, purified, and characterised using a variety of approaches. Nevertheless, contaminants including protein complexes, microvesicles, bacteria, etc. might make it difficult to separate exosomes during the isolation process.

Exosomes have crucial roles in the development of illnesses and cancer disorders. These nano-vehicles unquestionably play critical roles in leukaemia proliferation as well as angiogenesis, cell survival, and development.

Exosomes enriched with essential components that correctly alter the BM ecology to protect tumour cells from the immune system and chemotherapy drugs. MiRNAs have the most impact on the leukaemia process of all the cargos. A number of miRNAs, including miR-10b, miR-4532, miR-155, and miR-548ac, showed the ability to encourage the development of leukaemia by suppressing hematopoiesis. Contrarily, circular RNA-derived exosomes demonstrated a regulatory role in leukaemia cells' proliferation, motility, survival, and apoptosis. Additionally, several exosomal proteins, such as VEGFR, contribute to angiogenesis and increase the survival of AML cells.

The underlying mechanisms in exosome synthesis, pharmacokinetics, and biodistribution, however, still need to be further studied before being applied in clinical settings for acute leukaemia. Modified exosomes may also be a promising therapeutic candidate for lowering unfavourable side effects in exosome applications in the future, according to mounting research.

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Citethisarticle: Mary K & Lisa C. Exosomes Derived from Acute Myeloid Leukaemia (AML) have a Key Role in the development and survival of Tumors. Eur J Clin Oncol, 2022, 4(3), 34-35