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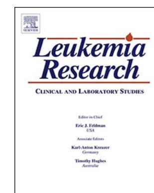

Invited review

Extracellular vesicles in leukemia

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ABSTRACT

Extracellular vesicles (EV) are nano-sized membrane enclosed vehicles that are involved in cell-to-cell communication and carry cargo that is representative of the parent cell. Recent studies have highlighted the significant roles leukemia EVs play in tumor progression, and ways in which they can lead to treatment evasion, thus meriting further investigation. Leukemia EVs are involved in crosstalk between the leukemia cell and its surroundings, transforming it into a cancer favorable microenvironment. Due to the diverse biological content found in leukemia EVs, they have an assortment of effects on the cells they interact with and can be harnessed as candidates for diagnostic and therapeutic treatments. This review focuses on EVs in the context of leukemia and the means by which they modulate their microenvironment, hematopoiesis, and the immune system to facilitate malignancy. We will also address current and prospective EV-based therapeutics.

1. Introduction

EVs are small, membrane-enclosed heterogeneous spheres of varying size that are directly secreted by all cells and carry a select cargo of cellular RNA, bioactive lipids, DNA and proteins that is usually representative of the parent cell [1,2]. EVs are present in physiological and pathological circumstances, and their numbers, cellular origin, composition, and function are cell type and disease dependent [3]. They are known for their coagulant phenotype but can also affect inflammation, angiogenesis, and intercellular signaling [4]. There is increasing evidence suggesting that these vesicles have an important role in the regulation of immune stimulation or suppression that can drive inflammatory, autoimmune, and infectious disease pathology [5]. Furthermore, EVs have the potential to alter the fate of their target cells by regulating gene expression, partially through epigenetic changes in the recipient cells [6].

The first line of evidence that tumor cells shed membrane-vesicles came in 1978 from studies performed by Friend and colleagues on samples obtained from patients with Hodgkin's disease [7]. In 1979, an independent study identified plasma-derived vesicles released by murine leukemia cells [8]. In the early 1980s, studies reported that EVs from pig hepatocellular carcinoma and mouse breast carcinoma cells were carriers of procoagulant activity. However, it was not until twenty years later that vesicles were acknowledged not to be artifacts but an active component of tumor microenvironment [9]. As in solid tumor malignancies, patients with hematologic malignancies have high levels of EVs in their biological fluids compared to normal controls that include cases of acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) [10,11]. Moreover, EV cargo also increases in patients with hematological malignancies [12,13].

EVs can be categorized based on their size. Microvesicles are 200–1000 nm in size and are formed by outward budding from the plasma membrane. Apoptotic bodies are 800–5000 nm in diameter and are released by cells undergoing programmed cell death [14]. More recently another category of EVs has been identified known as oncosomes that are much larger (1–10 µm) and are released as pinched membrane blebs from amoeboid cancer cells [15]. Exosomes are a subset of EV's reported to vary between 30 and 100 nm, although the exact size varies with isolation approach and cellular conditions. Whereas microvesicles form by budding from the plasma membrane followed by fission of their connecting membrane stalks, exosomes are formed by a combination of processes starting with the inward invagination of clathrin-coated microdomains on the plasma membrane, suggesting a more active sorting mechanism. The Endosomal Sorting Complex Required for Transport (ESCRT) System facilitates the development of the invaginated vacuoles carrying ubiquitinated cargos into

Abbreviations: EV, extracellular vesicles; ILVs, intraluminal vesicles; BMSCs, bone marrow stromal cells; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia; EGF, epidermal growth factor; HGF, hepatocyte growth factor; ATLL, adult T-cell leukemia/lymphoma; DLBCL, diffuse large B-cell lymphoma; HUVEC, human umbilical vein endothelial cells; MSCs, mesenchymal stem cells; GvHD, graft-versus-host disease; CAF, cancer associated fibroblasts; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; MSC-EVs, mesenchymal stem cell extracellular vesicles; VEGF, vascular endothelial growth factor; HTLV1, human T-lymphotropic virus type 1; Treg, regulatory T-cells

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early endosomes. A second invagination of vesicles termed intraluminal vesicles (ILVs) occurs into the endosomes where they accumulate into large multivesicular bodies [16]. From this point they may be trafficked to lysosomes or fused with the plasma membrane for the release of ILVs at which point they are referred to as exosomes [17]. Sorting of exosomes by the ESCRT involves several proteins that are subsequently used to identify them as exosomes including ALG-2-interacting protein X (ALIX) and tumor susceptibility gene 101 protein (TSG101) [18]. Other proteins most frequently associated with identification of exosomes are tetraspanins (e.g., CD9, CD63, and CD81) membrane transporters and fusion proteins (e.g., GTPases, annexins, and flotillin), heat shock proteins, lipid-related proteins, and phospholipids [19]. Exosomes are involved in numerous biological functions such as intercellular communication, antigen presentation, protein secretion, and RNA shuttling [20]. Exosomes can play a key role in physiological and pathological processes depending on the cell of origin that induce proliferation, differentiation, inhibition, quiescence or cellular death.

To isolate EV populations various methodologies have been implemented including ultracentrifugation, size exclusion chromatography, microfluidics, immunoaffinity capture based techniques, size-based techniques, precipitation, and more [21]. Each methodology exploits a particular trait of EVs including size, density or immunophenotype [21]. Some techniques combine several different methodologies in an effort to isolate purer populations [22]. Due to the specific advantages and disadvantages each method provides, there is no standardized method for EV isolation [23]. For the purpose of this review, exosomes and microvesicles are referred to as EVs because of the potential heterogeneity that results from the different isolation procedures [23].

Due to EV ability to contain a subset of specific molecules and antigens from the parent cell, there is increasing evidence suggesting that EVs can serve as biomarkers [24]. Tumor EVs contain unique genetic information about the tumor related to its state of malignancy, cellular type, and susceptibility to therapeutic treatment. As such, they may be used for early diagnosis and monitoring of cancer. Importantly, EVs are used by tumors to evade or influence their environment to favor tumor progression. These tumor derived EVs are implicated in modulating the tumor microenvironment [25], acting as immunomodulators [26], and contributing to inhibition of anti-tumor activity [27]. The complexity of the biology of EVs is just being discovered (Fig. 1). This review focuses on the role of EVs in the pathogenesis of hematologic malignancies and their potential utilization in therapies (Table 1).

2. Leukemia EVs

2.1. Leukemia EV content

AML EV content has been proposed to vary depending on the stage of disease and disease specific cell type [26]. Newly diagnosed AML patient plasma derived EVs, were shown to contain MICA/MICB, TGF-β1, myeloid blast markers (CD34, CD33, CD117), and a variety of microRNAs [10]. Other studies found that plasma-derived EVs in patients with AML carry the leukemia blast-relevant proteins CD34, CD44, CD96, CD123 and CLL-1 [13]. Hong and colleagues observed that TGF-β1 is found at higher concentrations in AML EVs when compared to non-disease patients. EVs were found to carry TGF-β1-associated propeptide and latency-associated proteins (LAP), PD-1, PD-L1, COX-2, FasL, or CD39/CD73 ectoenzymes which are known to alter functions of immune cells [22]. Classifying AML cell line MOLM-14 EVs via RT-PCR, Huan and colleagues identified FOXP3, ID1, GATA1, SHIP1, E2F1, CEBP-a and −b, Myc, and MEF2C. These transcripts are involved in hematopoiesis and/or leukemogenesis suggesting a developmental role in AML biology [28]. Patient AML blasts, primary $CD34^+$ bone marrow cells, and AML cell line derived EVs demonstrated the presence of 5 consistent candidate transcripts (NPM1, FLT3, CXCR4, MMP9, and IGF-IR) [28]. The consistency of biological material in EVs suggests that leukemia EV content is not simply a random assortment of cellular content.

Recently, Prieto and colleagues demonstrated that CLL EVs express different proteomic profiles in progressive and indolent CLL as well as in individuals at the time of disease onset and at progressive stages [29]. Similarly, Boysen and colleagues demonstrated that a specific marker subset of EVs was detected in a majority of post-therapy CLL patients and that this aspect can be used to study CLL progression [30]. Belov and colleagues utilized an antibody microarray (Dotscan) to compare the surface proteins of CLL cells with their EVs. Results indicated that EVs expressed approximately 40% of proteins detected on cells from the same patients. This included proteins (moderate or high levels of CD5, CD19, CD31, CD44, CD55, CD62L, CD82, HLA-A,B,C, HLA-DR; low levels of CD21, CD49c, CD63) that were not found on the EVs of healthy patients [31]. De Luca and colleagues observed that in CLL, EVs are found in greater numbers compared to healthy controls and that CD19 + and CD37+ B-cell derived EVs, correlate with high tumor burden [32]. Reiners and colleagues demonstrated that EVs from CLL patients contained disease-relevant mRNAs including the TCL1A oncogene and splicing factors that target the non-malignant environment [33]. Interestingly, Johnson and colleagues demonstrated that B-cell precursor acute lymphoblastic leukemia (ALL) cells release large EVs (< 6 μm) that contain intact organelles including mitochondria, lysosomes, Golgi and intermediate filaments [34]. Together these studies, propose that EVs may pose as promising biomarkers for leukemia progression, but there are multiple barriers that inhibit the ability to properly utilize them as such, including distinguishing between malignant cell-derived EVs from non-malignant cells [35].

2.2. Leukemia EV miRNA

Recent studies suggest that EVs transport a preponderance of non-coding RNAs that are relevant to AML pathogenesis. These non-coding RNAs influence transcripts relevant to AML prognosis (NPM1, FLT3-ITD), response to therapy (CXCR4, IGF-IR) and leukemic niche formation (IGF-IR, CXCR4, MMP9). Recently, Caivano and colleagues reported that miR-155 is found in higher levels in CLL, AML, and Waldenstrom's macroglobulinemia cases compared to controls [12]. Increased levels of miR-155 and miR-375 may be indicative of high risk of recurrence in AML patients [36]. In a study conducted by Kurre and colleagues, AML EVs showed statistically significant-fold increases in miR-155 and miR-375 relative to their parental cells, characteristics not observed in normal bone marrow EVs [28,37]. They also found substantial enriched concentrations of let-7a, miR-99b, −146a, −155, −191, and −1246, in concentrations of up to 1000-fold above cellular levels [28,37]. miR-155 has been consistently found to be upregulated in AML EVs and its functions are wide and diverse having 4174 putative human mRNA targets [28]. Together the differences observed suggest that miRNA cargo is not simply a random population of cellular content but a more active and specific process, although other interpretations may be inferred.

3. Leukemia EVs in the bone marrow microenvironment

Leukemia cells utilize EVs to transfer functional information to their microenvironment in amounts sufficient to alter intrinsic levels of respective molecules. The bone marrow niche is generally composed of osteocytes/osteoblasts/osteoclasts, the bone matrix, perivascular cells, quiescent hematopoietic stem cells (HSCs), sinusoidal endothelium, mesenchymal stem cells (MSCs), actively dividing HSC's, different stroma cells, and immune cells [38]. EVs exert pleiotropic biological functions via the transfer of bioactive molecules, including proteins, lipids, DNA, and RNA; consequently, modulating and reprogramming the bone marrow niche to promote their survival [39,40].

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