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Review Article

Extracellular Vesicles: A New Prospective in Crosstalk between Microenvironment and Stem Cells in Hematological Malignancies

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The bone marrow (BM) microenvironment in hematological malignancies (HMs) comprises heterogeneous populations of neoplastic and nonneoplastic cells. Cancer stem cells (CSCs), neoplastic cells, hematopoietic stem cells (HSCs), and mesenchymal stromal/stem cells (MSCs) are all components of this microenvironment. CSCs are the HM initiators and are associated with neoplastic growth and drug resistance, while HSCs are able to reconstitute the entire hematopoietic system; finally, MSCs actively support hematopoiesis. In some HMs, CSCs and neoplastic cells compromise the normal development of HSCs and perturb BM-MSCs. In response, "reprogrammed" MSCs generate a favorable environment to support neoplastic cells. Extracellular vesicles (EVs) are an important cell-to-cell communication type in physiological and pathological conditions. In particular, in HMs, EV secretion participates to unidirectional and bidirectional interactions between neoplastic cells and BM cells. The transfer of EV molecular cargo triggers different responses in target cells; in particular, malignant EVs modify the BM environment in favor of neoplastic cells at the expense of normal HSCs, by interfering with antineoplastic immunity and participating in resistance to treatment. Here, we review the role of EVs in BM cell communication in physiological conditions and in HMs, focusing on the effects of BM niche EVs on HSCs and MSCs.

1. Introduction

Normal hematopoietic stem cells (HSCs) reside in bone marrow (BM) and are supported by specialized and strictly organized stem cell niches, like endosteal and vascular [1]. The communication with other BM cells, including mesenchymal stromal/stem cells (MSCs), is crucial for HSC self-renewal, survival, and behavior. This dialogue within BM cell populations takes place through numerous extracellular and intracellular factors including hematopoietic growth factors and their receptors, signaling pathways, and cell cycle signaling [2].

Genetic alterations in HSCs or progenitors are associated to several hematologic malignancies (HMs) such as myelodysplastic syndrome (MDS), myeloproliferative neoplasia, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia [3]. Following genetic alterations, HSCs or progenitors are transformed into leukemia stem cells (LSCs) that retain self-renewal capability and uncontrolled

differentiation into leukemic blasts [4]. LSCs reside in the same niche as healthy HSCs and, on one side, they benefit from BM niche support and, on the other side, they modify the BM niche in order to induce a favorable environment for leukemic growth hampering normal hematopoiesis [5]. In addition, the interactions between LSCs and the endosteal niche sustain their silent state and protect them from the cytotoxicity of conventional chemotherapy [6, 7].

Studying the crosstalk between HSCs, LSCs, hematological neoplastic cells, and the BM microenvironment will enhance our comprehension of some human diseases including several HMs and the discovery of new potential therapies.

Extracellular vesicles (EVs) are emerging as new players in the intercellular communication and as new potential biomarkers for diagnosis and prognosis of human diseases [8–12]. They are a heterogeneous group of cell-derived vesicles including exosomes (Exo) and microvesicles (MVs) with a size ranging between 15 nm and 10 μm in diameter and with diverse biogenesis [13]. Different cells in physiological and pathological conditions, including tumor cells, can secrete EVs [14]. They act both in short-range intercellular communication, for example in the medullary microenvironment or in coculture conditions, and in long-range communication when released into the bloodstream through which they can reach secondary sites and give rise to premetastatic niches [15–17]. EVs carry part of DNA, RNA, proteins, lipids, and metabolites of the origin cells. Since EVs are present in biological fluids such as blood, urine, and sperm, [18, 19] and are a representative part of the whole cell for their phenotype and content, they could be used as a diagnostic tool by mimicking a "liquid biopsy." These last characteristics make them excellent candidates as diagnostic and/or prognostic biomarkers in different diseases, especially in tumors, through noninvasive or minimally invasive procedures. In our recent study, we found that serum EV number and their specific *oncomiRNA155* are higher in HM patients than in healthy subjects and, more importantly, EVs exposed specific tumor-associated surface markers [20, 21].

Stem cells (SCs) from embryos [22, 23], from different adult tissues such as BM, liver, and adipose tissue, and from induced pluripotent SCs, release EVs [24, 25]. Moreover, embryonic SC-EVs deliver mRNAs of pluripotent transcriptional factors such as HoxB4, Nanog, Oct3/4, and Rex-1, and transfer them to recipient cells, supporting hematopoietic progenitor cell expansion [26]. In addition, SC-EV microRNAs (miRNA) downregulate cell adhesion molecule levels, contributing to hematopoietic progenitor cell mobilization [27]. In a tumor context, SCs secrete EVs, which act as a means of communication in the tumor microenvironment playing multiple roles in tumorigenesis, and both in tumor angiogenesis and metastasis [28]. Finally, in *in vivo* models, SC-EVs mainly exhibit an inhibitory effect on the immune system suppressing proinflammatory processes and reducing oxidative stress and fibrosis [29]. Remarkably, MSC-EVs promote tissue renewal by inducing a proregenerative environment allowing stem and progenitor cells to successfully maintain tissue homeostasis. Importantly, MSC-EVs were used in two human disease therapies. In the first study, the administration of MSC-EVs reduces graft-versus-host disease (GvHD) symptoms and reduces steroid doses in an allogeneic transplantation of patients suffering from steroid refractory GvHD [30]. In the second study, the MSC-EV therapy triggers the regeneration within the affected kidney in patients with chronic kidney disease [31].

Although much has been reported about the stem cell and MSC-EV role, less is known about the influence of BM-EVs on HSCs and MSCs in physiological conditions and in malignancy onset, progression, and therapy resistance. In this review, therefore, we will discuss the recent advances in the field of EVs as actors in communication between cells within the BM niche in physiological conditions and in HMs, underlining the role and the effects in the tumor microenvironment-stem cell crosstalk. In particular, we will focus on the effects of EVs from BM niche cells on HSCs and MSCs.

2. Stem Cells

2.1. Hematopoietic Stem Cells (HSCs). HSCs are the only cells into the hematopoietic system that possess the potential for both pluripotency and self-renewal [1]. Pluripotency is the ability to differentiate into all functional blood cells; self-renewal is the ability to generate identical daughter cells without differentiation [32]. Postnatally, the BM is the primary site of HSC maintenance and hematopoiesis, but hematopoietic stress reallocates the niche to the spleen and induces extramedullary hematopoiesis. Although HSCs comprise only about 0.005–0.01% of the BM cell population, each single HSC retains the capability alone to reconstitute the entire hematopoietic system [33].

In AML, leukemia initiating cells (also named LSCs) represent a rare cell population that self-renews and generates an immature progeny invading and perturbing normal hematopoietic tissues [34]. HSCs and LSCs physically and functionally interact with the BM niche [35]. It is demonstrated that both HSCs and LSCs can be extended *in vitro* for a long time either in environmental conditions that mimic BM support or in coculture with BM stromal cells. These observations reinforce the crucial role that the BM niche, in particular the stroma, plays in healthy and leukemic stem cell homeostasis [5, 36–38]. It is still controversial whether cell-cell contact between hematopoietic stem/progenitor cells (HSPCs) and stromal cells is necessary to promote the hematopoietic cell expansion [39–43]; it is indeed clear that the definition of niche components and how they regulate hematopoiesis will provide the opportunity to improve regeneration after injury or HSC transplantation and to understand how disordered niche function could contribute to diseases, in particular to HMs.

2.2. Mesenchymal Stromal/Stem Cells (MSCs). The International Society for Cellular Therapy reported the minimal criteria for MSC definition: (i) they adhere to plastic under standard culture conditions; (ii) they express CD73, CD90, and CD105; (iii) they lack the expression of CD45, CD34, CD11b or CD14, CD19 or CD79a, and HLA-DR; and (iv) they have the potential to differentiate into the osteogenic, chondrogenic, and adipogenic cell lineages [44, 45]. MSCs

may be isolated from BM, umbilical cord, liver, adipose tissue, and multiple dental tissues [46, 47]; here, we will focus on MSCs derived from BM. They maintain long-term, quiescent HSCs through the presentation of surface signals and the secretion of major stemness supportive cytokines such as leukemia inhibitor factor and IL-6 [48, 49].

On the contrary, MSCs from leukemic patients hamper *in vitro* hematopoietic cell expansion and differentiation. In particular, AML-patient MSCs significantly impair the expansion of human umbilical cord blood $CD34^+$ progenitors and limit their differentiation to maintain a stable pool of immature quiescent precursors ($CD34^+$ $CD38^-$) compared to healthy donor-derived MSCs (hereafter healthy MSCs) [50]. Remarkably, healthy MSCs maintain AML patient blasts in a quiescent state resulting in increased leukemic survival after treatment with cytarabine [51]. Overall, MSCs have a functional role in the regulation of the BM microenvironment, in particular by influencing the immune system and angiogenesis and in supporting hematopoiesis [52–55] and, consequently, they are widely used in allogeneic hematopoietic stem cell transplantation [56, 57].

However, much work remains in defining the relationship between MSCs, HSCs, and other niche cells, especially on how they interact with each other and how these interactions regulate the hematopoiesis. Uncovering how the microenvironment participates in normal and HM progression will enhance new approaches to hematological disorders.

3. Extracellular Vesicles

On the basis of biophysical properties (i.e., size and shape) and the mechanism of biogenesis, EVs are classified into Exo, MVs, apoptotic bodies, and oncosomes [58, 59].

Exo are the smallest EVs (20–150 nm) that are generated inside multivesicular bodies which are secreted after their fusion with the plasma membrane [60, 61]. They show a higher rigidity of their lipid bilayer compared with that of cell membranes, making them resistant to degradation and useful as vehicle of different biomolecules. The formation and the release of Exo take place through both endosomal sorting complex required for transport-dependent or -independent mechanisms [60, 61].

MVs enclose EVs with a more heterogeneous size (50–1000 nm) bud directly from the plasma membrane and, for this reason, their surface markers are largely dependent on the composition of the membrane from which they derive [59].

Apoptotic bodies are membrane blebs that are released during cell apoptosis [62] with a diameter ranging between 50 nm and 5 μm, contain DNA binding histones, and are depleted in glycoproteins [63, 64].

Lastly, oncosomes are the largest EVs (1–10 μm in size) produced by membrane protrusions of malignant cells that lug bioactive molecules involved in the progression of cancer [64, 65].

The release of EVs from donor cells can be constitutive or be induced in response to activation or stress signals [64], including glucose and intracellular Ca^{2+} concentrations, oxygen tension, and microenvironmental pH [66]. Interestingly, EVs contain cargos of diverse nature including nucleic acids (i.e., mRNA, noncoding RNA such as miRNA, transferRNA, and genomic and mitochondrial DNA), cytosolic and membrane proteins, lipids, cellular organelles like mitochondria [67, 68], and metabolites [69, 70]. Interestingly, some databases such as EVpedia, Vesiclepedia, and ExoCarta collect the currently known components of EVs [71–73].

Notwithstanding, the content of EVs generally reflects the nature and the status of the donor cell: EVs could be enriched or depleted of specific materials with respect to origin cells [64, 74]. Likewise, EV cargo nature and abundance are also influenced by the pathways that lead to the formation of different EV subtypes [75].

The total cargo of human MSC-EVs is recently defined by next generation sequencing and proteomic analyses. They are enriched in proteins that support tumor (PDGFR-β, TIMP-1, and TIMP-2), lipids (sphingomyelin and diacyl-glycerol), metabolites (glutamic and lactic acid), several oncomiRNAs (*miRNA21* and *miRNA34a*) [76], critical surface markers, and signalling molecules characteristic of MSCs [77]. A recent work reports that BM-MSC-Exo are highly enriched in transferRNAs that represent more than 35% of the total small RNAs, while miRNAs account for only 2–5% [78]. This composition differs in MSC-Exo released from other tissues. In addition, BM-MSC-EVs contain a pattern of miRNAs essential for the metabolism, proliferation, differentiation, and homing of SCs [79]. Additionally, different chemokines, such as MCP-1, IP-10, and SDF-1, are found in BM-MSC-Exo in multiple myeloma (MM) [62]. These chemokines are important in supporting MM cell viability.

3.1. EV Uptake from Recipient Cells. Once released, EVs reach recipient cells where they exert pleiotropic effects through distinct signalling cascades via autocrine, paracrine, and juxtacrine feedback loops [80].

EVs can be internalized into recipient cells with different mechanisms including endocytosis, direct cell surface membrane fusion, and a lipid raft-mediated energy-dependent process, or they can remain permanently associated with plasma membrane [81].

Surface molecules, such as integrins or receptors, and microenvironment conditions control the EV uptake by regulating their specific cell tropisms, while EV cargo, released into target cells, alters their composition by inducing phenotypic, functional, and epigenetic modifications [17, 82].

In particular, the specific integrin-mediated adhesion of tumor Exo to specific cell types and organs induces the metastatic niche formation [83]. Similarly, BM dendritic cell Exo are preferentially internalized by splenic conventional dendritic cells, rather than by B-lymphocytes, macrophages, or splenic T cells [84]. Moreover, Exo from mantle cell lymphoma cells are preferentially taken up by themselves while only a minor fraction of Exo was internalized into T-cell leukemia and BM stroma cell lines [85]. The specific cell type uptake of EVs has also been observed *in vivo*. In fact, human MSC-EVs injected into the blood stream of mice primarily accumulated in the liver, spleen, and in sites of acute kidney injury, where they facilitated injury recovery [86]. Similarly, melanoma-derived Exo accumulated in the lungs, bone, liver,

and spleen and they increased the frequency of metastasis at these sites [87]. Finally, Parolini et al. reported that low pH favors Exo uptake by melanoma cells [88].

4. Role of EVs in Physiological BM Niche

As reported, MSCs are commonly studied as EV donor cells. EVs from BM-MSCs shuttle the selected molecular cargo to recipient cells targeting genes involved in organogenesis, cell survival and differentiation, tissue regeneration, immunomodulation, and angiogenesis [79, 89–91]. Nevertheless, the role of MSC as EV target cells must not be ignored. In fact, EVs derived from differentiated cells are able to modulate the MSC phenotype [92]. In particular, miRNA contained in EVs released from neuronal [93], endothelial [94–96], and kidney epithelial [97] cells induce proliferation, migration, and secretion of soluble factors in MSCs.

Immune cells, such as monocytes, use EVs to communicate with MSCs modulating their phenotype by upregulating osteogenic gene expression [98]. In fact, Ekström et al. demonstrated that both RUNX2 and BMP-2 expression is significantly increased in MSCs after monocyte-EV stimulation, whereas no significant difference is observed in osteocalcin [99], an osteoblastic gene regulated by BMP-2 via RUNX2 [100].

Regarding the hematopoietic system, Ratajczak et al. demonstrated that, besides coagulation, MVs derived from activated platelets play a role in important biological processes. In particular, these last enhance the chemotactic responsiveness of HSPCs, and increase their survival and proliferation by transferring specific mRNA and proteins [101]. In another study, the same authors reported that EVs released from embryonic SCs sustain HSPC stemness and multipotency by delivering specific "stemness" mRNAs [101].

More recently, it was demonstrated that mRNA and miRNA in mast cell EVs have been transferred to $CD34^+$ progenitors. In fact, Ekström et al. identified, by using miRNA microarray analysis, 116 miRNAs in Exo and 134 in donor mast cells. Furthermore, microarray experiments revealed the presence of approximately 1800 mRNA in Exo, which represent 15% of the donor cell mRNA content. Transfer experiments reveal that Exo could shuttle RNA between human mast cells and $CD34^+$ hematopoietic progenitor cells suggesting their role in cell communication [102].

A recent discovery showed that stromal cells release biologically active EVs which act on HSPCs. Specifically, two murine stromal cell lines, one with and the other without HSPC supportive capacity, produce different EV types in terms of size and of small RNA and mRNA signature. $Lin^-Sca1^+cKit^+$-HSPCs preferentially take up EVs produced by a supportive stromal line (suppEVs) but not those released by a nonsupportive one. SuppEVs transfer mRNA and miRNA in $Lin^-Sca1^+cKit^+$-HSPCs by modifying their gene expression profile. Importantly, suppEVs maintain the survival and clonogenic potential of $Lin^-Sca1^+cKit^+$-HSPC by inhibiting their apoptosis [103]. Collectively, these data assert that EVs constitute an important novel communication system in mediating the HSPC-supporting capacity of MSCs.

5. EV Role in BM Niche of Hematological Malignancies

It is now clear that BM cell populations, including malignant cells, influence the tumor microenvironment, via autocrine [104] or paracrine mechanisms through the secretion of soluble factors including EVs [105]. In HMs, neoplastic EVs promote tumor progression via an autocrine loop which includes interacting with their producing malignant cells, supporting autosustainability, and increasing aggressiveness [58, 105]. This relevant cross-talk mechanism is clearly demonstrated in MM [106], in pre-B acute lymphoblastic leukemia [107], in erythromyeloblastoid, and CML [108].

EVs from resistant neoplastic cells can transfer drug resistance to sensitive cells in AML [109, 110]. In particular, EVs from apoptosis-resistant AML cells modulate the expression of apoptosis-associated proteins in chemotherapy sensitive blasts [109]. A multiresistant AML cell line transfers, through EVs, chemoresistance to sensitive acute promyelocytic leukemia cells [110].

BM-MSC derived EVs induce survival, proliferation, and migration of MM cells *in vitro* and *in vivo* in a mouse model [111, 112]. Finally, Exo from AML MSCs and not from healthy MSCs protected a leukemic cell line carrying FLT3 internal tandem duplication from treatment with a specific FLT3 inhibitor [113].

HM-EVs exert also the immune modulation effects; malignant EVs inhibit natural killer cell cytotoxicity, promote T cell apoptosis, and enhance immunosuppressive activity of myeloid-derived suppressor cells *in vitro* and *in vivo*. These EV effects are reported in B and T cell lymphomas [114, 115], CLL [116], AML [117], and MM [62, 118, 119]. Overall these data support the idea that there is indeed a complex and intriguing EV-mediated cross talk between malignant cells and BM cells that defines a favorable neoplastic microenvironment. In this context, we summarize the role of HM niche EVs on SCs and MSCs in Figure 1.

5.1. HM Niche EVs versus SCs. Different studies reported that Exo released from AML cell lines impair hematopoiesis by suppressing HSPC clonogenicity and by reprogramming stroma [120, 121]. According to Razmkhah et al., BM-AML-MVs promote the survival of healthy HSCs by inducing leukemic molecular characteristics, like high level of *miRNA21* and *miRNA29* [122]. Interestingly, an essential role of VPS33B in Exo pathways in HSCs and in leukemia development at early stage was demonstrated. In fact, its deletion in an *in vivo* AML model impairs the maturation and secretion of Exo and delays the AML onset [123]. Interestingly, MVs released from LSCs enhance proliferation, migration, and inhibition of apoptosis of AML cells. LSC-MVs containing a high level of *miRNA34a* inhibits the effects of LSCs on AML cells [124, 125].

Muntion et al. suggested that MVs derived from MSCs of MDS patients modify $CD34^+$ cell properties, promoting their cell viability and clonogenic capacity and altering their miRNA and gene expression profiling [126].

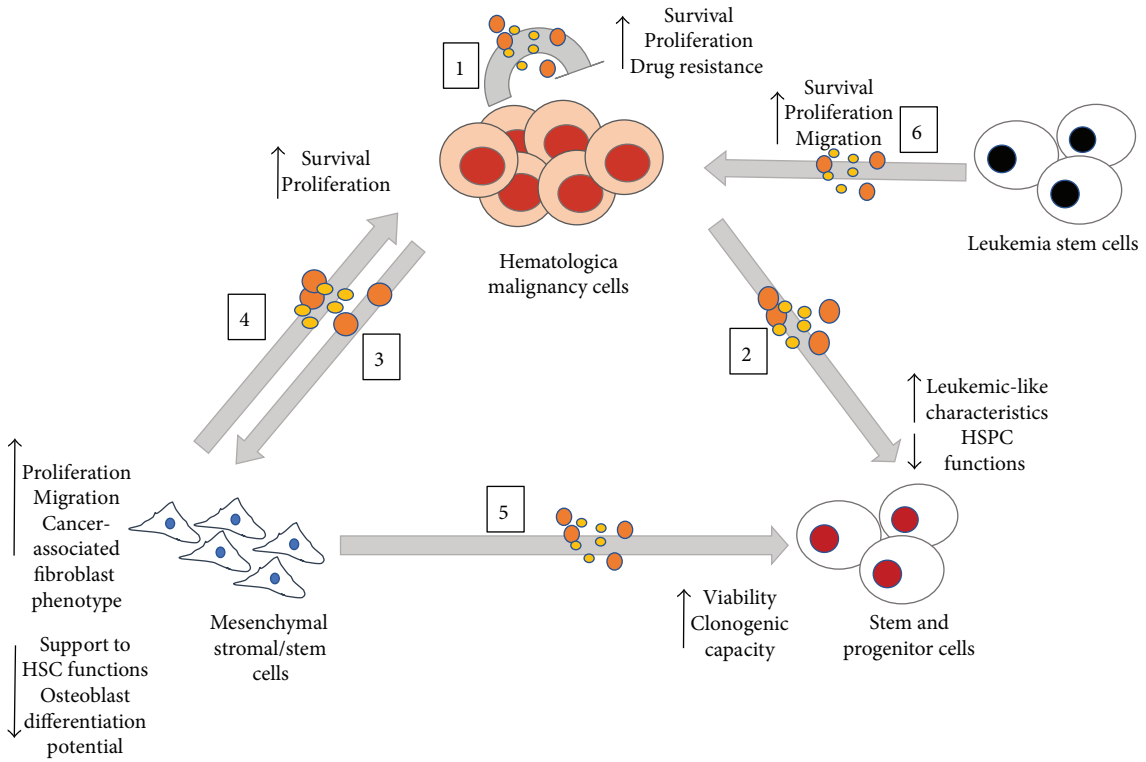

Figure 1: A schematic drawing of neoplasm EV effects in BM of HMs. Tumor EVs (colored balls) can (1) render malignancy more aggressive through autocrine mechanisms via (2) the induction of a suppression of hematopoietic stem/progenitor cell (HSPC) functions and a stem cell malignant transformation and (3) modification of mesenchymal stromal/stem cells (MSCs) reducing their HSC support. On the other hand, "reprogrammed" MSCs release EVs that (4) support the proliferation of malignancy cell proliferation and (5) promote HSPC viability and clonogenicity. In addition, leukemia stem cell EVs induce proliferation and migration of malignant cells (6). Arrows turned upwards (∧) and downwards (∨) indicate an increase and a reduction, respectively.

EVs released by myeloproliferative neoplastic MSCs, enriched in *miRNA155*, induce an increase of granulocyte colony forming unit number in neoplastic $CD34^+$ cells [127].

Collectively the reported studies show that the leukemia niche, in terms of LCSs and MSCs, is able to deregulate normal HSCs and neoplastic cells by EV-mediated communication.

5.2. HM Niche EVs versus MSCs. In the tumor context, MSC-EVs have a controversial role: they can promote or inhibit the tumor progression. These opposite effects of MSC-EVs can likely depend from both MSC source and culture conditions [128–130].

In general, EVs from healthy cells have a beneficial effect on recipient cells; on the contrary, EVs from cancer cells, have a detrimental influence also on MSCs [131]. MSCs exposed to tumor EVs acquire a series of functions such as migration to the tumor site [54, 132], production of proinflammatory cytokines [133], induction of prometastatic niches [134, 135], promotion of tumor growth *in vivo* [130], epithelial-to-mesenchymal transition induction [136, 137], recruitment of neoplastic cells in the BM [138], improvement of angiogenesis [139, 140], and modulation of the immune system [141–143].

Intriguingly, the crosstalk between tumor cells and MSCs seems to occur with a certain sequence: tumor cells, through EVs, communicate and modify MSCs; these reprogrammed MSCs, in response, produce EVs that can return on cancer cells or other cells creating a favorable environment for tumor [144, 145].

In HMs, less is known about the effect of neoplastic EVs on MSCs.

In CLL, Ghosh et al. found that MVs play an important role in the activation of the microenvironment in favor of disease progression [146]. CLL-MVs can activate the AKT signaling pathway in BM-MSCs by inducing the production of vascular endothelial growth factor, an important element for CLL cell survival [147]. In addition, Paggetti et al. demonstrated that CLL-derived Exo induce an inflammatory phenotype in endothelial cells and MSCs resembling the phenotype of cancer-associated fibroblasts [148]. In this way, leukemic Exo create a favorable environment for promoting CLL progression.

Exo derived from adult T-cell leukemia/lymphoma cells induce changes in cellular morphology and promote proliferation in MSCs by transferring epigenetic regulators, like *miRNA21* and *miRNA155* [149].

Horiguchi et al. found that EV *miRNA7977* derived from AML/MDS $CD34^+$ cells, is transferred into BM-MSCs where it reduces the poly binding protein 1 levels by compromising their ability to support $CD34^+$ cells [150]. Huan et al. studied the role of Exo in developing the BM AML niche [151]. They

reported that leukemic Exo are taken up by BM stroma. These Exo deliver important AML pathogenesis mRNA such as FLT3, NPM1, IGF-IR, and CXCR4. In addition, they carry *miRNA150* which binds the receptor for SDF-1 and CXCR4 mRNA. Consequently, these Exo reduce the expression of CXCR4 and thus cell migration versus SDF-1 of target cells. The CXCR4/SDF-1 axis is fundamental for HSPC retention in BM and their differentiation. The last AML-Exo effects are an altered proliferation and migration of BM-MSCs and hematopoietic progenitor cell lines, by reprogramming the BM microenvironment [151].

Recently, Kumar et al. showed that, in *in vitro* and *in vivo* models, AML-Exo are internalized by BM cells, increase long-term HSC population, and alter stromal compartment [152]. They induce the osteoblast inhibitor DKK1 expression in MSC progenitors decreasing their osteoblast differentiation potential. AML-EVs reduce the expression of factors that support normal hematopoiesis such as CXCL12, KITL, and IL-7 in MSCs. These modified stromal cells enhance leukemia growth at the expense of normal hematopoiesis [152]. In another context, Exo released by CML cells stimulate BM-MSCs to produce IL-8, which, in turn, promote both *in vitro* and *in vivo* leukemic cell survival [153]. MVs containing "leukemic" transcripts from CML cells transfer these mRNAs in healthy MSCs, increasing their proliferation [108]. Finally, *miRNA146a* in EVs from MM cells is transferred in MSCs inducing the secretion of elevated levels of cytokines which improved both MM cell viability and migration [154].

Collectively, the reported data demonstrate that EVs derived from HM cells are efficiently transferred into MSCs to transform the BM microenvironment into a niche that supports malignancy at the expense of HSCs, although the mode of transformation is still uncertain.

6. Conclusions

In conclusion, EVs constitute a new bidirectional communication system between BM microenvironment and SCs. In fact, SCs, including HSCs and MSCs, are not only EV donors but also targets of EVs derived from BM cells. Specifically, immune cells communicate with MSCs via EVs modulating their phenotype. In addition, EVs represent a tool in mediating the MSC capacity to support HSPCs, improving their survival and clonogenic potential in physiological conditions.

In different HMs, EVs are significantly induced compared to healthy controls. Neoplastic EVs exert oncogenic functions that (1) boost malignancy through autocrine signaling, (2) induce a suppression of HSPC functions and SC malignant transformation, (3) modify the BM environment in favor of cancer/leukemic cells acting also on MSCs. These last cells exposed to tumor EVs acquire a series of functions such as migration to the tumor site, production of proinflammatory cytokines, induction of prometastatic niches, promotion of tumor growth *in vivo*, recruitment of neoplastic cells in the BM, improvement of angiogenesis, and modulation of the immune system. Overall, "tumor modified" MSCs release EVs that play an active role in supporting a favorable environment for malignant cells at the expense of normal hematopoiesis.

In order to render more transparent the field of EVs, an EV-TRACK platform is created to collect biological and technical information of EVs [155]. Further studies are needed to clarify not only the mechanism of action of EVs in disease and health, but also to define EV population-specific identity and cell origin, and the standardization of protocols for their isolation and characterization.

Conflicts of Interest

The authors declare no conflicts of interest.

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