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Chapter

Roles of Extracellular Vesicles in Cancer Metastasis

Eman Helmy Thabet

Abstract

Extracellular vesicles (EVs) are biological active vesicles and carriers of information in intercellular communication. In cancer settings, EVs especially exosomes (Exo), play a focal role in modulating the tumor microenvironment mainly by increasing tumor proliferation, facilitating the crosstalk between tumor and tumor-neighboring cells, and influencing the host immune response. Amongst these functions in tumor growth, Exo modulate fundamental steps of tumor progression, such as growth, invasion, and immune modulation. On the endocrine level, Exo released from tumors were shown to mediate distant cell-cell communication processes via secretory factors and miRNAs, which result in the set-up of pro-tumorigenic microenvironments supportive of metastatic dissemination. This is achieved through processes such as fibroblast activation, extracellular matrix ECM production, angiogenesis, and immune modulation.

Keywords: tumor microenvironment, exosomes, tumor progression, metastasis, targeted therapy

1. Introduction

Extracellular vesicles (EVs) are traditionally classified into three types: exosomes (Exo), microvesicles (MVs), and apoptotic vesicles. Several theories exist on how tumor cells alter their neighboring cells and matrix ultimately changing their behavior into an invasive one. This typically would involve the transport of materials from tumor cells to their adjacent surroundings. These materials include a wide range of soluble cytokines, RNA species, enzymes, and proteins. Most of which are carried in nano-sized carriers such as EVs. EVs are classified according to their size and the mechanism of genesis. The first class of EVs known as MVs or when secreted from cancer cells, are called oncosomes [1]. MVs formation is originated by the outward budding of the cell surface at specific regions along the plasma membrane enriched with high concentrations of lipids, such as cholesterol and glycosphingolipids, and proteins such as Flotillin-1 and 2 [2]. Exo represent the second major class of EVs [3]. They are formed when multivesicular bodies (MVBs) in the endo-lysosomal pathway accumulate intraluminal vesicles (ILVs) that consist of proteins and nucleic acids. Exo are smaller in size and range from 30 to 50 nm.

EVs can function in an autocrine, paracrine, and even endocrine fashion, and were shown to impact various cancer cell phenotypes, increasing their cell growth and promoting metastasis [4]. This secretome is released into the microenvironment and acts as cell-cell communicators. Tumor derived Exo (TDE) has appeared as imperative facilitators in cancer initiation, progression, metastasis, host immune

suppression, and drug resistance [5]. TDE typically consists of high sphingolipids and cholesterol contents that contain major histocompatibility complex (MHC) molecules, heat shock proteins, and tetraspanin (CD63, CD81, and CD9). Additionally, tumor antigens such as Mart1, gp100, TRP, and Her2-neu have been discovered in TDE [5]. TDE also contains surface and soluble proteins and RNA species such as mRNAs and miRNAs. mRNAs conveyed in EVs result in proteins synthesis in target cells, while miRNAs alter their gene expression [6]. The *protein cargo* of TDE includes extracellular matrix (ECM) proteins, cell adhesion proteins, cell-surface receptor tyrosine kinases, chaperones, cytosolic and nuclear signaling proteins, as well as DNA and RNA binding proteins. Several types of nucleic acids that have been identified in EVs include RNA transcripts, microRNAs, long non-coding RNAs (lncRNAs), and DNA [7].

2. The role of MVs/TDE regional preconditioning

Tumor development is a multistep process that starts by cellular reprogramming of cells to acquire the hallmarks of cancer cells to gain and maintain abnormal growth and invasive capacity [8]. The complex process of tumor formation and spreading additionally requires a rewiring of the surrounding stromal cells. This can be induced by intrinsic cell events such as genetic or epigenetic aberrations or by external factors from direct or indirect cell communication [9]. In cancer, EVs especially Exo, have been shown to be essential for various steps during tumor initiation and progression. EVs disrupt signaling and gene expression regulation in the recipient cell by horizontally transferring bioactive chemicals between cancer cells and the surrounding stroma. As a result, malignant cells can change the phenotype of surrounding benign cells to one that supports tumor growth and metastasis, creating a favorable environment for cancer progression and spread. EVs play several roles in priming the surrounding environment preparing it for metastasis and invasion. The role of EVs in promoting tumor progression has been elucidated in studies on mixed populations of EVs. The function of EVs largely depends on their bioactive cargo, in particular the shuttling of tumor-specific proteins to the surrounding cells. While researchers have mainly studied the RNA content of EVs, however, the focus is starting to shift towards the EVs proteome [10].

The protein content of MVs within mixed populations of EVs was discovered to be significantly diverse from that of the Exo proteome, and is supplemented in proteins involved in microtubule, actin, and cytoskeleton networks, ARF6, its effector phospholipase D2, and parts of the endosomal sorting complex required for transport family (ESCRT-I) [11] By transporting these molecules, MVs can impact nearby tumor cells and stromal cells.

2.1 MVs mediated tumor-invasion

One example in which MVs shed by the cancer cells were shown to enhance tumor cell proliferation is in multiple myeloma. This effect was shown to be related to the amelioration of the Extracellular Matrix Metalloproteinase Inducer (EMMPRIN/CD147) on the tumor MVs. This protein is known to be overexpressed in solid tumors, some lymphomas, and leukemias [12]. Another study in breast cancer cells found that the highly glycosylated version of EMMPRIN exists in high quantities in breast cancer cell-derived MVs and enhances tumor invasion through activation of p38/MAPK signaling [11]. Interestingly, it was found that MVs from patient Blood with metastatic breast cancer had a similar high-EMMPRIN expression, along with the tumor marker Mucin-1 (MUC1/CA 15-3) [11]. Additionally,

the truncated oncogenic form of the epidermal growth factor receptor (EGFR), EGFRvIII, commonly expressed in aggressive brain tumor cells, is associated with pro-tumorigenic tumor–tumor crosstalk via MVs. It was discovered that EGFRvIII was present in MVs released by U373 glioma cells, allowing them to transfer malignant features from highly aggressive tumor cells to the more benign tumor cells, EGFRvIII-negative, thereby facilitating their oncogenic transformation [11]. Hence, MVs are convenient communicators within the TME, as they can either mediate the horizontal transfer of oncogenic material or activate oncogenic signaling pathways in neighboring cancer cells, enhancing their survival, proliferative, and angiogenic potential and triggering their transformation into an aggressive phenotype.

2.2 Tumor-immune cells crosstalk

Alongside the tumor–tumor communication, MVs were proven to facilitate the crosstalk between the tumor and its surrounding stroma and immune cells which ultimately leads to cancer immune evasion. In breast cancer cells, the secretion of both tumor MV and TDE induced the expression of Wnt5a in tumor-associated macrophages. Macrophage Wnt5a promoted ß-catenin-independent Wnt signaling in breast cancer cells when delivered by macrophage-derived MVs and Exo, resulting in enhanced tumor invasion. This shows how EV-based cell-cell communication can drive tumor-associated immune cells to stimulate tumor growth [11]. MVs-enriched preparations induced the differentiation of monocytes producing anti-inflammatory cytokines such as IL-10. In line with this, early stimulation with tumor MV triggered macrophage polarization towards an anti-inflammatory phenotype with decreased anti-tumor cytotoxic potential. Additionally, as T cells represent the first line of the immune defense, tumor cells appear to suppress T cell activity and diminish antitumoral immune response via MVs-mediated cell-cell communication. For instance, leukemia-derived MVs deliver miRNAs to T cells, which alters T cell phenotype [13] (**Figure 1**). Moreover, MVs released by irradiated breast cancer cells were shown to carry abundant immune-suppressive proteins, such as programmed cell death ligand 1 (PD-L1) which inhibited cytotoxic T cell activity and enabled tumor growth (**Figure 1**) [14].

2.3 TDE-mediated epithethelial mesenchymal transition

TDEs, through their miRNAs proteins, DNAs, mRNAs lncRNAs, initiate the transformation of epithelial cells to mesenchymal cells. This transformation was due to the loss of epithelial E-cadherin expression, cell-cell adhesion and cell polarity, and gaining of vimentin expression [16].

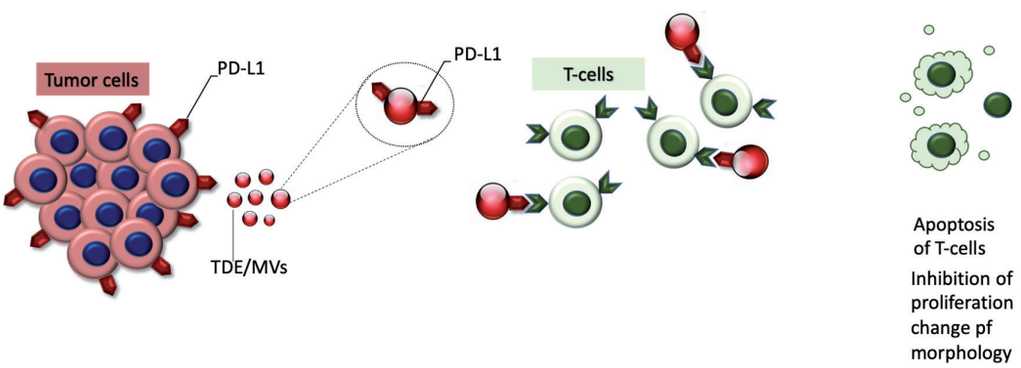

Figure 1.
Exosome PD-L1 (similar to tumor PD-L1) can bind to PD-1 on T cells, induce T cell apoptosis, and inhibit T cell activation and proliferation [15].

3. Pre-metastatic niche formation

The complex and heterogeneous microenvironment of both primary or metastatic tumor is comprised of a network of cellular and acellular constituents. The cellular compartment consists of tumor cells and assorted non-transformed cells, such as cancer-associated fibroblasts (CAFs), macrophages, and endothelial cells. The non-cellular part is formed by secreted factors and components of the ECM. The tumor microenvironment modulates tumor progression by providing inhibitory or stimulatory growth signals [17]. Thus pre-metastatic niche refers to the microenvironment, that is primed to allow tumor cells to colonize in and disseminate to distant sites. The main machineries of the premetastatic niche formation include tumor-derived secreted factors (TDSFs), EVs bone marrow-derived cells (BMDCs), suppressive immune cells and host stromal cells [4], and inflammation. Chronic inflammation is a driving force for tumor development and metastasis. Thus, the local inflammatory microenvironment is one of the essential factors for the pre-metastatic niche formation and driving force for metastasis.

3.1 TDE in upregulation of inflammatory molecules and premalignant niche formation

Tumor development and metastasis are aided by chronic inflammation. As a result, one of the most important variables in the establishment of a pre-metastatic niche is the local inflammatory microenvironment. Tumor cells can be induced to create TDSFs such as vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α), transforming growth factor (TGF-β), and interleukin-2 by the local inflammatory microenvironment. These TDSFs then exert a paracrine effect on myeloid cells, initiating their migration to potential pre-metastatic niche formation sites [18]. Host stromal cells in the pre-metastatic niche may upregulate the expression of inflammatory factors in response to TDSF activation. The recruitment of BMDCs or immune cells to the pre-metastatic niche speeds up the release of inflammatory factors. Exo from tumors also transport inflammatory substances into the bloodstream, where they reach the pre-metastatic niche. In the pre-metastatic niche, an inflammatory milieu supportive to tumors is eventually generated [18].

In a study conducted by Hoshino, he showed that the proinflammatory cytokine s100 was upregulated up to four folds when Kupffer cells were treated with integrin intact Exo, as compared to those treated with integrin knocked out Exo. Hoshino speculated that the activation of Src, and its phosphorylation might be a causative pathway [19].

3.2 Cellular compartment of the pre-metastatic niche

3.2.1 Cancer-associated fibroblasts

TDE and MV were also shown to modify fibroblasts in the tumor stroma. When normal human fibroblasts were exposed to oral squamous carcinoma derived MV [20] the fibroblasts were altered into a cancer phenotype. This switch to CAFs was largely mediated via metabolic reprogramming of the fibroblasts to aerobic glycolysis, with an increase in glucose uptake and lactate secretion. Some TDEs contain surface TGF-β along with betaglycan, which could trigger SMAD-dependent signaling and regulate the differentiation of fibroblasts to myofibroblasts [21]. This was further proved by co-culturing the generated CAF with cancer cells

which led to enhanced cancer cell invasion and migration, creating a bidirectional cross-talk that favors tumor promotion and spread. The MVs-induced fibroblast activation and spreading seem to occur in the matrix milieu in the tumor periphery [22]. In prostate cancer, TDE were shown to induce the expression of RANKL and Metalloproteinases in CAFs, through miR-100, -21, and -139, further promoting its metastasis [23]. Hypoxia seems to stimulate prostate cancer cells to release protein-rich Exo which further induces activation of CAFs [24], promotes epithethelial mesenchymal transition (EMT), stemness, and angiogenesis by prostate cancer cells.

Additionally, TDE were also described as regulators of metabolism in the tumor microenvironment, for example, breast cancer tumors could suppress glucose uptake by lung fibroblasts, via secretion of Exo containing miR-122, increasing glucose availability and facilitating metastasis [25]. The cell-to-cell communication mediated by Exo is also affected by the genetic profile of the recipient fibroblasts. For example, fibroblasts lacking the BRCA1, a tumor suppressor gene, internalize larger amounts of serum-derived Exo when compared to BRCA1 containing fibroblasts [26]. Furthermore, these cells were found to undergo a malignant transformation when exposed to Exo derived from sera of cancer patients, implying that oncosuppressor genes can prevent exosome information from tumor cells from being integrated and thus shelter these cells from their pro-oncogenic signals [26].

3.2.2 Macrophages and immune cells

Tumor MVs extravasate through the vessel wall in pancreatic cancer, reach the liver microcirculation and are picked up by perivascular macrophages to prime the liver metastatic niche in a CD36-dependent manner. Furthermore, tumor MVs produced from the B16F10 melanoma cell line was discovered to cause metastases in BALB/c mice, which are generally resistant to the B1610 tumor cell line [27]. TDEs also protect cancer cells from apoptosis by selectively effluxing apoptosis inducer proteins that are delivered by T cells or natural killer (NK) cells. TDEs also reduce the effects of therapy by preventing drug efflux or concealing the binding site of monoclonal antibodies, which could lead to the emergence of chemotherapy-resistant cell populations [28].

Exosome-derived programmed death receptor 1 (PD-1) and programmed death-ligand 1 have been linked to an immunological escape mechanism in recent years. PD-1 is mostly found on macrophages, activated T cells, and B cells, whereas PD-L1 is abundant in tumor tissues, antigen-presenting cells (APCs), and stromal cells [29]. T lymphocytes can recognize and destroy tumor cells in normal circumstances. When PD-1 attaches to PD-L1, however, it sends an inhibitory signal to T cells, causing them to die and inhibiting their activation and proliferation. As a result, blocking the PD-1/PD-L1 pathway may boost the immune response by increasing the killing effect of T cells [30]. T lymphocytes can recognize and destroy tumor cells in normal circumstances. When PD-1 attaches to PD-L1, however, it sends an inhibitory signal to T cells, causing them to die and inhibiting their activation and proliferation (**Figure 1**). As a result, blocking the PD-1/PD-L1 pathway may boost the immune response by increasing the killing effect of T cells. As a result, Exo containing PD-L1 suppress the immune system in the pre-metastatic milieu and promote the establishment of a pre-metastatic niche [31].

3.2.3 Endothelial cells and vascular barriers

Angiogenesis within the primary tumor is also influenced by tumor MVs and TDE. Normal endothelial cells (ECs) were shown to endocytose tumor EVs, which

triggered PI3K/Akt signaling and increased EC motility and tube formation ability [32]. Tumor MVs and TDE also release VEGF, a pro-angiogenic substance that stimulates ECs [33]. Similarly, MVs produced from multiple myeloma cells have been demonstrated to transfer CD138, a myeloma cell marker, to ECs, promoting their proliferation, invasion, and production of the angiogenic mediators IL-6 and VEGF, resulting in tube formation [50] (**Figure 2**). MVs change the environment around the main tumor and create pre-metastatic niches from afar. This was originally attributed to their procoagulant activity, which encouraged the production of microthrombi and facilitated the extravasation of trapped circulating tumor cells. ECs are important components of the tumor microenvironment because they provide a pathway for nutrients and trophic substances [34].

3.2.3.1 Neovascularization

TDE enriched in vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 has been demonstrated to regulate the process of neovascularization in myeloid leukemia [35]. Furthermore, enhanced vascularization has been linked to the packaging of miR-92a in Exo derived from leukemia[36] and CO-029/D6.1A Tetraspanin in Exo produced from pancreatic cancer [37]. Upregulation of Heparanase in tumor cells, such as myeloma and breast malignancies, has also been linked to increased exosome production and exosomal packing of Syndecan-1, VEGF, and hepatocyte growth factor, resulting in enhanced endothelial invasion through the ECM [38]. Exo produced from skin cancer can also enhance angiogenesis by transferring the EGFR [39] and miR-9 to ECs [26]. Furthermore, melanoma-derived Exo have been found to condition sentinel lymph nodes prior to the installation of melanoma cells and subsequent metastasis by upregulating Collagen 18 and Laminin 5, as well as producing angiogenic growth factors [26].

Another significant component in altering tumor-EC communication is hypoxia. Hypoxic glioblastoma cells, for example, release Exo that interact with ECs, promoting proliferation and angiogenesis both in vitro and in vivo [40], and also prompting tissue factor/Factor VIIa dependent activation of hypoxic ECs [26].

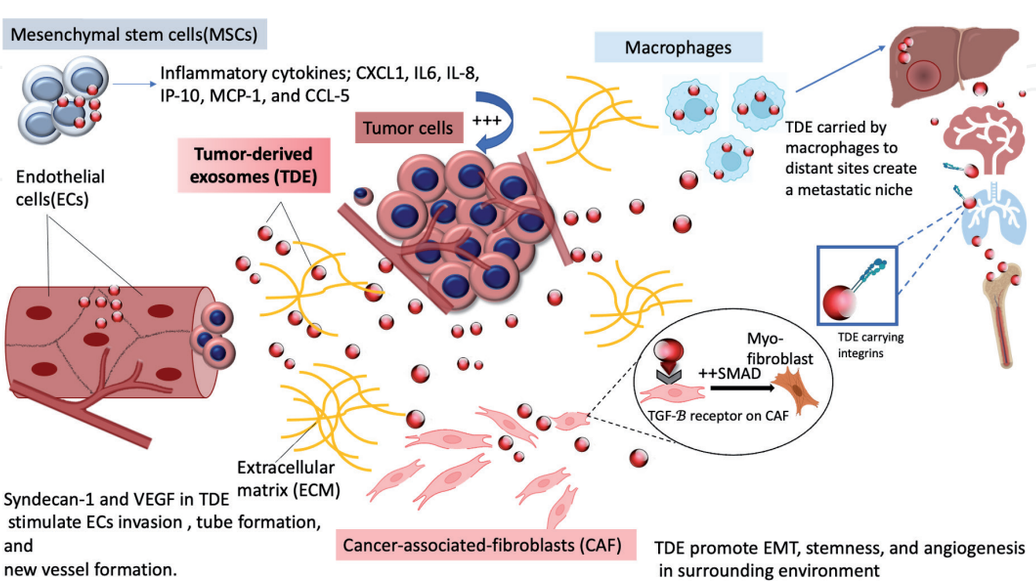

Figure 2.
Possible mechanisms of pre-metastatic niche formation. The figure delineates how TDEs can modulate its surroundings of ECM, cancer-CAFs, immune cells, ECs, and MSCs all in favor of tumor support and progression. TDE can carry integrins to distant sites and create a pre-metastatic niche.

3.2.3.2 Vascular leakage

Exo from melanoma cause pulmonary vascular leakiness and upregulate tumor cell recruitment genes such Stabilin 1, Vitronectin, Integrins, and Ephrin receptor b4 in lymph nodes, forming pre-metastatic niches [41]. Furthermore, breast cancer-derived Exo enriched in miR-105 alter the expression of Claudin 5, Zonula Occludens protein 1, and Occludin, which promotes metastasis by disrupting vascular endothelial barriers [42]. Exo produced from brain tumors include miR-181c, which regulates EC actin dynamics and promotes the breakdown of the blood-brain barrier by three times. Protein Kinase-1 Degradation Requires Phosphoinositol [43]. Similarly, glioblastoma cells release Exo with high quantities of VEGF-A, which promote EC permeability and angiogenesis in vitro [44].

3.2.4 Tumor-stem/progenitor-non-transformed cell communication

TDE can promote pro-tumorigenic microenvironments via promoting tumor-stem/progenitor cell contact, in addition to its well-known actions in differentiated cells. Melanoma-derived Exo, for example, stimulate BMDCs by transferring the oncoprotein MET, resulting in the mobilization of vasculogenic and hematopoietic bone marrow progenitor cells to ensure vascular proliferation and immunosuppression at pre-metastatic niches [45]. Communication between tumor stem/progenitor cells is also critical in bone metastasis. Exo from bone metastatic prostate cancer PC3 cells were found to influence the process of bone metastasis by modulating both osteoclast genesis and osteoblast proliferation. Exo generated from osteoblasts, on the other hand, have been demonstrated to stimulate PC3 prostate cancer cell proliferation [46].

TDE was also demonstrated to influence the development of myeloid precursor cells into myeloid-derived suppressor cells (MDSCs), which are known to aid tumor progression by permitting immune escape [47]. Exo produced from breast carcinomas have been found to be taken up by bone marrow cells and to convert these cells' development pathways toward MDSCs via Prostaglandin E2 and TGF-β, boosting COX2, IL6, VEGF, and Arginase1 accumulation by MDSCs [48].

TDE can also cause alterations in mesenchymal stem cells (MSCs), which help to promote and maintain tumor-promoting inflammatory environments. For example, HSP70+ lung tumor-derived exosomes (TDEs) activate NF-kB and cause MSCs to secrete IL-6, IL-8, and MCP1 via TLR2-mediated signaling, causing MSCs to become more inflammatory and tumor supportive [49]. According to De Veirman et al. [50], myeloma-derived Exo transfer miR-146a to mesenchymal cells, stimulating them to secrete numerous cytokines and chemokines including CXCL1, IL6, IL-8, IP-10, MCP-1, and CCL-5 (**Figure 2**). Another example is Exo produced by KMBC cholangiocarcinoma cells, which cause MSCs to upregulate IL-6, and hence KMBC cell proliferation [51].

4. Mechanisms of TDE in tumor metastasis

4.1 Tumor cell proliferation and anti-apoptotic effect

One of the proposed mechanisms of tumorigenicity of TDE is the induction of tumor cell proliferation. Studies involving various cancer cells such as, chronic myeloid leukemia and in human gastric cancer, showed that this proliferative potential is via an autocrine induction through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and MAPK/ERK signaling pathways. Additionally, through the transference of lncRNAs (reviewed in [49]).

In addition, glioblastoma-derived Exo were shown to induce proliferation of the human glioma U87 cell line [40] in a mechanism dependent on the chloride intracellular channel protein 1 (CLIC1) [52]. In a more specific context linked to prostate cancer treatment, prostate cancer LNCaP cells grown in the presence of androgens generate Exo high in CD9, which enhance the growth of androgen-depleted LNCaP cells. Another example involves the promotion of in vivo growth of murine melanomas by systemic treatment of mice with melanoma-derived Exo, which accelerated growth and inhibited apoptosis of melanoma tumors in vivo [26].

4.2 Invasiveness and motility

TDE can alter the migratory behavior of recipient malignant cells. Exo produced from nasopharyngeal cancer-bearing EMT-inducing signals such as TGF-β and hypoxia-inducible factor 1 alpha (HIF1a) [53], matrix metalloproteinases (MMPs) Notch1, LMP1 Casein Kinase II and Annexin A2, were shown to enhance the migratory capacity of the tumor recipient cells. Another example involves Exo derived from hypoxic prostate cancer cells, which prompted invasiveness and motility of naïve human prostate cancer cells (reviewed in [26]) through the neighboring stroma and to nearby cells.

4.3 Chemoresistance

Exo have been found to have a role in tumor-tumor communication by transferring chemoresistance. Exo have been linked to the transfer of Docetaxel resistance in prostate cancer since Corcoran and colleagues first discovered it [54]. The transfer of cisplatin resistance in lung cancer is achieved by donor resistant cells producing Exo with low levels of miR-100-5p, which leads to enhanced expression of the mammalian target of rapamycin (mTOR) protein and chemoresistance in recipient cells [55].

MiRNA packed in Exo from drug-resistant cells can modulate the expression of specific target genes in breast cancer, such as miR-23a targeting Sprouty2, miR-222 targeting PTEN, miR-452 targeting APC4, and miR-24 targeting p27, thereby modulating chemoresistance in recipient cells that integrate these Exo. In fact, exosomal miR-222 plays a key role in this process, as the silencing of miR-221/222 prevents the transmission of resistance [56].

In addition to miRNAs, the transfer of exosomal mRNAs that encode drug-resistant proteins may result in chemoresistance in the receiving cell. GSTP1 exosomal mRNA from Adriamycin-resistant breast cancer cells, for example, confers resistance to previously susceptible cells. The presence of GSTP1 in circulating Exo from patients' peripheral blood was linked to a worse outcome in breast cancer patients receiving Adriamycin [57]. A supporting stroma is required for an optimum metabolic and physiological environment for tumor growth. Fibroblasts are the most abundant cells in most solid tissues, participating in environmental cue responses and being a common target of tumor-derived signals [58].

4.4 Integrins in metastasis

Integrins are a wide family of cell adhesion receptor proteins such as alpha-3beta1, alpha6beta1, alpha6beta4, and alpha7beta1. Their roles have been implicated in tumor metastasis and mesenchymal transformation. TDE carry these integrins from primary tumor sites to distant sites such as lung, lymph nodes, brain, and bone creating pre-metastatic niches (**Figure 2**) [59].

5. Clinical applications of TDE

TDEs are involved in the advancement of several forms of cancer. Because of their abundance, TDEs may serve as noninvasive diagnostic and prognostic tools for various cancers. Additionally, blocking exosome secretion can slow the growth of some malignancies. Hence, Exo have been a popular target for developing cancer treatment techniques because of this property. Decreasing the expression of the exosomal proteins, Rab27a and Rab27b, inhibit exosome secretion without matching changes in soluble proteins secretions [60]. Several drugs used in the pharmaceutical industry such as Ketoconazole (an anti-fungal) sphingomyelinase (a hydrolase enzyme that is responsible for degrading sphingomyelin) [61], are additionally Rab27a inhibitors. These drugs can be re-directed as cancer modulators for their possible effects on attenuating TDE tumor progressive effects.

Furthermore, TDE owing to its small size, cancer-homing, and nontoxic nature, TDE can be re-directed to serve as a drug delivery system. Exo have been proven in several investigations to act as drug delivery vehicles, transporting anti-cancer chemicals to target cells [62]. For example, adriamycin and paclitaxel, target cancer cells via exosomal encapsulation and have low toxicity and immunogenicity [63].

6. Conclusions

EVs modulate the environment that favors tumor growth and progression. EVs provide a method of cell-cell communication, and through their rich cargo of ECM proteins, cell adhesion proteins, tyrosine kinases, chaperones, signaling proteins, DNA and RNA binding proteins, they create a pre-metastatic niche. By priming nearby and distant cells into becoming cancerous, they promote tumor metastasis. Several mechanisms have been discovered for their actions including, promotion of migratory behavior, chemoresistance, anti-apoptosis, vascular leakage, and immune modulation. Understanding how TDE and MVs create a pre-metastatic niche and how halting the trafficking of such vesicles can produce a revolutionizing new era in the field of cancer therapeutics. By preventing TDE-promoted metastasis and tumor progression, coupled with conventional radio and chemotherapy, the survival rates of cancer patients can significantly improve.

Conflict of interest

The author declares no conflicts of interest.

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