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Extracellular vesicles: important collaborators in cancer progression

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Abstract

Extracellular vesicles (EVs) are membrane vesicles that are released from cells and mediate cell-cell communication. EVs carry protein, lipid, and nucleic acid cargoes that interact with recipient cells to alter their phenotypes. Evidence is accumulating that tumor-derived EVs can play important roles in all steps of cancer progression. Here, we review recent studies reporting critical roles for EVs in 4 major areas of cancer progression: promotion of cancer invasiveness and motility, enhancement of angiogenesis and vessel permeability, conditioning premetastatic niches, and immune suppression.

Introduction

Cells modify their environment and communicate with other cells by many mechanisms, including direct cell-cell contact and secretion of soluble proteins. Recently, release of extracellular vesicles (EVs) from cells has been identified as a major way that cells communicate. While originally thought to be released only from specialized cells (1–3), the past decade has shown that EVs are released not only from all cell types in the human body, but also from virtually all organisms, including bacteria, and parasites (4–10). EVs are referred to by a variety of names including exosomes, microvesicles (MVs), ectosomes, microparticles, and large oncosomes. Generally, the term exosome refers to EVs that are small membrane vesicles (30–150 nm in diameter), formed by vesiculation of intracellular endosomal multivesicular bodies (MVBs) and released by exocytosis (11). MVs, ectosomes, microparticles and large oncosomes are all terms that refer to EVs that bud and are released from the plasma membrane. While exosomes are the most commonly studied type of EV to date (12, 13), increasing recognition of the diversity of EVs is expanding the scope of the field and leading to identification of new functional roles for various types of EVs. For the purposes of this review, we will generally refer to EVs that are shed from the plasma membrane as MVs, noting that these EVs can be of various sizes, including in the same size range as exosomes (30–150 nm) (14–16), intermediate size (150 nm-1 μm) MVs (7, 17, 18), and large oncosomes (>1 μm) (19–21).

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EVs have surface molecules that allow them to interact with target cells (22–24). After binding to cells, EVs may modify the physiological state of the recipient cell by directly inducing signaling or alternatively by delivering their internal contents via endocytosis, phagocytosis or fusion with the target cell's plasma membrane (22, 25–27). EVs carry a variety of bioactive molecular cargoes, such as nucleic acids (DNA, mRNA, microRNA [miRNA], and other non-coding RNAs), proteins (receptors, transcription factors, enzymes, extracellular matrix (ECM) proteins), and lipids that can affect the function and phenotype of recipient cells in diverse ways (7, 25, 28–33).

Recent studies conducting proteomics, lipidomics, and RNA-seq analyses have identified differences in the composition of these bioactive molecular cargoes among diverse types of EVs (34–37). For example, small EVs (typical "exosome" preparation purified at 100,000xg) were found to be enriched in heparin-binding proteins and receptors, including integrins, compared to larger EVs (typical MV preparation purified by centrifugation at 10,000xg), suggesting that they might interact with different target cell populations (34). Likewise, recent studies have found different RNA populations in EVs, with full-length mRNAs >1 kb in length preferentially found in the large EV preparations compared with small EV preparations (36, 38). Although much more characterization of the differences between EV types should be performed, these data suggest that in many cases, the type of EVs may determine which EVs interact with distinct target cells and the functional consequence of those interactions.

One area of intense research is cancer EVs, due to early identification of their role in the tumor microenvironment. In this review, we discuss EV-mediated functions in cancer progression including the classic steps of tumor metastasis and roles in tumor immunity.

Function of EVs in cancer metastasis

Facilitation of tumor cell motility and invasiveness

A first and critical step in cancer metastasis is acquisition of an invasive migratory phenotype, which enables cancer cells to invade surrounding tissue and intravasate into blood and lymphatic vessels. This phenotype involves structural changes of the cancer cell, especially reorganization of the cytoskeleton to form dynamic actin-based invasive structures such as lamellipodia, invadopodia, and amoeboid blebs (39, 40). In addition, changes in the surrounding environment such as altering the phenotype of surrounding non-tumor cells can also greatly contribute to promotion of invasion.

EVs have been shown to carry molecules that enhance migration, and invasion, including matrix metalloproteinases (MMPs), ECM molecules, and growth factors (41–57). Our group found that exosome secretion takes place at matrix-degrading actin protrusions called invadopodia (47) and is critical for invadopodia function, including invadopodia formation, stabilization, and ability to degrade ECM. Notably, we found that exosomes purified from head and neck squamous cell carcinoma (HNSCC) cells carry key invadopodial proteinases, including MT1-MMP and MMP2 (47). Consistent with this finding, secretion of MT1-MMP at invadopodia was found to require the endolysosomal SNARE VAMP7 (58). However, MT1-MMP on exosomes is not critical for the ability of those exosomes to drive invasion

through Matrigel (48). In a separate study, we found that autocrine secretion of exosomes also drives cellular motility, in part by carrying fibronectin, which enhances adhesion formation and speed of cancer cells (46). Additional studies have shown that exosomes enhance cancer cell adhesion, motility and invasion (44, 49–51, 59), suggesting that these are major functions of exosomes. In addition, directional sensing of migrating cells has been shown to be dependent on exosome secretion in both cancer cells and neutrophils, suggesting a universal mechanism (46, 54, 60).

MVs have also been shown to carry MMPs and ECM molecules, indicating a diversity of mechanisms by which invasion-promoting molecules can be sorted to EVs (42, 43, 53, 55, 56). For MT1-MMP, delivery into MVs involved association of VAMP3 with the tetraspanin CD9 (43). In some cases, these MVs were shown to directly promote anchorage independent growth (an ECM-sensitive phenotype) and invasion through Matrigel and gelatin (53, 55, 56). In contrast to exosomes, MVs have been shown to be associated with amoeboid motility, downstream of RhoA activation (61). Expression of the constitutively-active G14V mutant of RhoA leads to increased MV blebbing and shedding and induces amoeboid morphology (61), which relates to tumor invasiveness (39, 62). Secretion of tumor-derived large oncosomes also may relate to amoeboid movement (63–65) in that siRNA targeting or chromosomal deletion of Diaphanous-Related Formin 3 (DRH3) affects nonapoptotic blebbing and the release of large oncosomes by changing cortical actin (20) and also affects amoeboid motility.

In addition to an autocrine role for EVs in driving cancer cell migration and invasion, many studies have identified a role for paracrine interactions with host cells in this process. Cancer-derived exosomes are known to convert fibroblasts to an activated myofibroblastic “cancer-associated fibroblast” (CAF) phenotype (66–69). This could increase cancer cell motility by a variety of mechanisms, including synthesis and reorganization of collagen fibers to promote migration (70–75). In addition, fibroblast-secreted exosomes were shown to promote breast cancer cell (BCC) protrusive activity and motility via induction of Wnt-planar cell polarity (PCP) signaling (49). CAF exosomes carrying ADAM10 can also promote cell motility by activating Notch and RhoA signaling in cancer cells (76). Mesenchymal stem cell (MSC)-derived exosomes were reported to promote migration and invasion of gastric cancer cells (77), by activating Akt signaling to induce epithelial-mesenchymal transition and transwell invasion. Finally, CAFs have been reported to deliver miRNAs via EVs that induce aggressive cancer cell phenotypes such as invasiveness, motility, EMT, anchorage-independent cell growth, or drug resistance that could lead to future metastasis (78, 79).

Besides fibroblasts, additional cell types release EVs that facilitate cancer cell invasiveness. This may occur in an ongoing “conversation” via EVs. For example, miR25–3p and miR-92a-3p carried in liposarcoma-derived exosomes were shown to stimulate secretion of IL-6 from tumor-associated macrophages - through miRNA-mediated activation of NF-kB signaling - which in turn promoted liposarcoma cell invasion (80). In ovarian cancer, both chemical inhibition experiments and studies with purified exosomes indicate that exosomal transfer of CD44 to human peritoneal mesothelial cells facilitates cancer invasion. Upregulation of CD44 in the mesothelial cells promoted secretion of MMP9 to directly

disrupt the mesothelial barrier (81). Notably, transfer experiments using exosomes purified from control or CD44-knockdown (KD) ovarian cancer cells demonstrated the dependence of the mesothelial cells on exosomal transfer of CD44 for the upregulation of pro-MMP9 secretion (81). Whether the mesothelial MMP9 was actually carried on EVs, as has been shown in other systems (48, 55, 82) was not addressed.

Adipocyte-derived exosomes have been shown to promote migration and invasion of cancer cells (83, 84). In one study, a mechanism was identified and related to alteration of metabolic pathways in the recipient cancer cells (83). Proteomic analysis of the adipocyte exosomes identified multiple proteins associated with fatty acid oxidation (FAO); in the presence of these exosomes, FAO was increased in the melanoma cells. Inhibition of this metabolic pathway completely abrogated the exosome-mediated increase in migration. In obese mice, both the number of exosomes secreted by adipocytes as well as their effect on FAO-dependent cell migration were amplified compared to lean mice. Also in humans, the number of adipose tissue-derived exosomes was positively correlated with body mass index and exosomes from obese individuals increased melanoma migration compared to exosomes from lean individuals.

Platelet-derived EVs (PDEVs), also known as microparticles, have been shown to promote lung cancer cell invasiveness (85), suggesting a role for chronic inflammation and potentially feedback from procoagulant properties of cancer cells. PDEVs transferred integrin CD41/aIIb and stimulated the phosphorylation of MAPK p42/44 as well as the expression of MMP2, MMP9 and MT1-MMP in lung cancer cell lines. In addition to promoting trans-Matrigel chemoinvasion, the PDEVs also increased *in vivo* metastasis, potentially by “coating” the cells and enhancing invasion at distant sites. Additional studies have shown that PDEVs enhance *in vitro* invasive behavior and correlate with poor patient outcome ((86) and additional studies reviewed in (87)).

Several remaining issues exist for the function of EVs in tumor cell motility and invasiveness. EVs clearly play an important autocrine role in cell motility and invasion, but the mechanisms are not fully understood. For example, exosomes are known to play a role in cancer cell chemotaxis, but unlike in neutrophils, the responsible exosome cargoes are unknown (46, 54, 60). In addition, the role of EV-associated versus plasma membrane or soluble proteinases in mediating matrix degradation is unclear. For paracrine interactions, the diversity of stromal cells in different organs is high. Thus, it seems likely that there will be a concomitant diversity in EV cargo content and in regulation of tumor cell motility and invasiveness. In addition, in some organs - such as gastrointestinal or skin tissue - the types of stromal cells encountered depend on the organ’s layer structure. A challenge for the future is to understand the role of EV-mediated tumor-host crosstalk in the context of different tissue content and structure.

Role of EVs in promoting angiogenesis and permeability of endothelial cells

Intravasation of tumor cells is a critical step in cancer metastasis that can be enhanced by EVs. A number of studies have shown that EVs enhance both angiogenesis and vascular permeability, which could explain the known “leakiness” of tumor vasculature and enhance cancer intravasation (88–91).

Brain tumors are notoriously vascular and a number of studies have shown that glioma-derived EVs can increase angiogenesis. EVs secreted from glioblastoma cells carry angiogenesis-related proteins such as IL-6, IL-8, angiogenin and IGFBP1, especially under hypoxic conditions, and promote *in vitro* and *in vivo* angiogenesis (92, 93). GBM MVs carrying EGFRvIII also induce VEGF expression in endothelial cells, dependent on the presence of EGFRvIII in the MVs (94). In addition to brain tumors, EV protein cargoes, including carbonic anhydrase 9, annexin II, myoferlin, and WNT4, have been reported to enhance angiogenesis for a number of other tumor types (95–98). Compared to angiogenesis, lymphangiogenesis is relatively understudied. However, the lymphatic mucin podoplanin was shown to be incorporated into both MVs and exosomes released from HNSCC cells and to promote lymphatic vessel formation (99). This lymphangiogenesis is related to podoplanin-mediated regulation of Rho signaling (100). Interestingly, few studies have identified VEGF itself as a key EV cargo promoting angiogenesis, although some studies reported that VEGF is carried together with other angiogenic components in EVs (101–104). Instead it appears that EVs may synergize with the well-established role of soluble secreted VEGF family members by carrying additional angiogenic cargoes.

In addition to carrying proteins, EVs carry a number of extracellular RNAs. Of these, miRNAs have been the best studied and a number of these have been suggested to be involved in promoting tumor angiogenesis. An initial report that provided direct evidence of EV-mediated proangiogenic miRNA delivery showed that leukemia-derived exosomes deliver miR-92a into endothelial cells and promote angiogenesis (105). Exosomes purified from leukemia cells transfected with Cy3-labeled miR-92a were taken up by endothelial cells. The miR-92a-containing exosomes enhanced endothelial cell migration and tube formation compared with control exosomes. miR-92a has been shown to induce angiogenesis by downregulation of a5 integrin in endothelial cells (106), although in some cases miR-92a can also inhibit angiogenesis (107, 108). Exosomal transfer of miR-135b has also been shown to promote endothelial tube formation (109). miR-135b is known to promote angiogenesis by suppressing Factor Inhibiting Hypoxia inducible factor-1 (FIH-1) (110). Exosomes purified from hypoxic multiple myeloma cells decreased FIH-1 expression in endothelial cells and increased endothelial cell tube formation. The biologic effects of the purified exosomes were inhibited by expression of anti-miR-135b and augmented by overexpression of a miR-135b mimic in the parental cells. A number of other miRNAs have also been implicated in regulating tumor angiogenesis via exosomal transfer, although in many cases direct causality has not been shown (89, 111–117).

EVs have also been shown to increase vascular permeability. Similar to angiogenesis, both protein and RNA cargoes have been shown to promote vascular leakiness. Schillaci reported that metastatic tumor-derived exosomes promoted endothelial permeability more than non-metastatic tumor-derived exosomes (118). They also showed that metastatic tumor-derived exosomes were enriched for activators of RhoA/ROCK signaling, which may destabilize endothelial junctions. Co-treatment of endothelial cells with tumor-derived exosomes and a ROCK inhibitor reverted the stability of endothelial cell-cell junctions. In lung cancer, delivery of exosomal miR-23a to endothelial cells inhibited expression of the tight junction protein ZO-1, thereby increasing vascular permeability and cancer transendothelial migration (112).

Remodeling of target organs to facilitate engraftment and development of metastases.

After arrival of cancer cells in target organs, successful engraftment and growth of cancer cells requires the appropriate microenvironment. As with their role in enhancing survival at primary sites, EVs also modify microenvironments in distant organs to prepare “metastatic niches” (28, 119, 120).

The “premetastatic niche” was originally defined by David Lyden’s laboratory, in a landmark paper showing that secreted factors from melanoma cells could select sites of metastasis (e.g. the lung) in part by recruiting VEGFR1+-producing bone marrow-derived cells to those sites as well as induction of FN deposition by stromal cells (121). Subsequently, the mystery factors secreted from the melanoma cells were demonstrated to be exosomes (122). Exosomes from highly metastatic melanomas educated bone marrow-derived cells (BMDCs) toward a pro-vasculogenic and pro-metastatic phenotype through transfer of the receptor tyrosine kinase protein MET. Reducing Met expression in exosomes diminished the pro-metastatic behavior of bone marrow cells. Inhibition of exosome secretion via Rab27a RNA interference prevented bone marrow education and reduced tumor growth and metastasis. In another organ system, the same group showed that pancreatic cancer-derived exosomes induce liver pre-metastatic niche formation in naive mice and consequently increase liver metastatic burden (123). Uptake of pancreatic cancer-derived exosomes by Kupffer cells caused transforming growth factor β (TGF β) secretion and upregulation of fibronectin production by hepatic stellate cells, which enhanced metastasis.

In addition to enhancing tumor growth and engraftment at distant sites, exosomes appear to select the specific location of tumor metastasis. That is, where the exosomes lodge, so do the tumors – in an updated version of the seed-soil hypothesis (124). The cargo on EVs is likely important for the selective interaction with target cells and organs via ligand-receptor interactions. Indeed, for metastatic niche selection, specific integrins expressed on tumor-derived exosomes were shown to correlate with organ-specific metastasis (125). Exosomes from pancreatic cancer cell lines that metastasize primarily to the liver expressed αvβ5 integrin and colocalized with Kupffer cells in mouse livers after *in vivo* injection. Likewise, exosomes from human breast cancer cell lines that metastasize primarily to the lung expressed α6β4 and α6β1 integrins, and co-localized with S100A4-positive fibroblasts and surfactant protein C (SPC)-positive epithelial cells. KD of integrin β5 or β4 led to reduced uptake of the KD exosomes by the liver and lung, respectively, and integrin β4-KD exosomes were unable to promote metastatic seeding of breast cancer cells to the lung. Since integrins are ECM receptors, these data suggest that the exosomes are either binding to ECM at the metastatic sites or carrying ECM that then mediates binding to cognate receptors on host organ cells. Future studies are likely to define these mechanisms in more detail and define whether other integrins are involved in metastatic niche preparation.

Additional groups have fleshed out diverse mechanisms by which cancer-derived EVs enhance metastatic niche formation. CD105+ EVs secreted from renal cancer stem cells were shown to promote blood vessel-rich premetastatic niches, potentially by transfer of proangiogenic miRNAs and mRNAs (126). miR-122-carrying breast cancer EVs were shown to promote premetastatic niche formation in the brain and lung by modulating

glucose metabolism in brain astrocytes and lung fibroblasts (127). Interestingly, miR-122 is a predictive marker of metastasis in breast cancer patients (128) and secreted from breast cancer. The increased metastasis of breast cancer cells induced by miR-122-overexpressing EVs was reduced by inhibition of miR-122 in the parent cells (127). Tumor-derived EVs can also drive bone metastatic niche formation. Amphiregulin (AREG) carried on non-small cell lung cancer (NSCLC) exosomes was shown to induce EGFR pathway activation in pre-osteoclasts that in turn causes increased expression of RANKL and differentiation into osteoclasts, triggering the so-called “vicious cycle” of osteolytic bone metastasis whereby factors released from bone destruction enhance tumor growth (129, 130).

Lymph nodes are also a major site of cancer metastasis. In sentinel lymph nodes, melanoma exosomes were shown to enhance seeding of melanoma cells, potentially by increasing gene expression in the lymph nodes of multiple molecular factors that promote melanoma cell recruitment, ECM deposition, and vascular proliferation (131). In another study, pancreatic exosomes were shown to seed lymph nodes and the lung dependent on exosomal expression of CD44 (132).

On the other hand, EVs can play an inhibitory role in metastasis. For example, exosomes from nonmetastatic melanoma cells can inhibit metastasis of aggressive melanoma cells by inducing immune surveillance at metastatic sites (133). Compared with exosomes purified from isogenic metastatic cells, exosomes purified from nonmetastatic cells induced expansion of patrolling monocytes (133), which are CD45+, $Ly6C_{low}$, and CX3CR1+ cells that act in the microvasculature to scavenge debris and reduce inflammation (134, 135). Patrolling monocytes had previously been found to limit metastasis to the lung by recruiting and activating NK cells and to “scavenge” EVs (136, 137). The exosomes from nonmetastatic melanoma cells also induced differentiation of macrophages to an M1 phenotype, and activation of NK cells. Pigment epithelium derived factor (PEDF) on the melanoma exosomes was found to be a key molecular cargo, both altering immune phenotypes to inhibit metastasis in mice and correlating with human melanoma patient survival. Of note, exosomes from nonmetastatic cells that were knocked-down for PEDF were much less potent in their ability to inhibit metastasis than control exosomes from the same cells. An anti-PEDF antibody also reversed the effect of “nonmetastatic” exosomes on induction of immune cytokine expression by RAW 264.7 macrophages. Interestingly, exosomes isolated from nonmetastatic patient serum inhibited experimental metastasis in mouse models, whereas exosomes isolated from metastatic patient serum had the opposite effect (133).

In addition to cancer-derived EVs, EVs released from host cells at metastatic sites also regulate establishment of tumor metastasis. In the brain, astrocyte-derived exosomes transfer PTEN-targeting miR-19a to metastatic tumor cells (138). The resultant PTEN loss leads to increased secretion of the chemokine CCL2, which in turn recruits myeloid cells that enhance the outgrowth of brain metastatic tumor cells. In the bone marrow, mesenchymal stem cell (BM-MSC)-derived exosomes were shown to promote dormancy of metastasized breast cancer cells (139). Breast cancer cells treated with BM-MSC exosomes had a dormant phenotype including a low proliferation rate and chemotherapy-resistance. From the miRNAs increased in BM-MSC exosomes compared to adult fibroblast exosomes, miR-23b

was identified and its overexpression in breast cancer cells was demonstrated to induce dormancy phenotypes including downregulation of CD44 expression, enhancement of dormancy gene expression, and decreased *in vivo* proliferation.

From these reports, it is clear that EVs can influence the microenvironment at future metastatic sites and in many cases promote organ-specific metastasis.

Regulation of tumor immunity

The immune system is a powerful regulator of tumor progression (140). To escape this regulation and survive, tumor cells have evolved diverse mechanisms, including some that utilize EVs (30–32, 141, 142). In this section, we discuss the role of EVs in regulating diverse immune cell types, including anti-tumor cytotoxic cells and immune regulatory cells, and their potential role in modulating the response to immune checkpoint blockade therapy.

Role of EVs in cytotoxic lymphocyte regulation

CD8+ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are major cytotoxic immune cells that target and kill cancer cells (140, 143–147). The presence of these cells in tumors is associated with good prognosis in a number of tumor types (148). Tumor-specific CD8+ CTLs and NK cells eliminate tumor cells through the production of apoptosis-inducing molecules or cytotoxic granules, such as granzyme and perforin (144, 147). Though the field is still new, a number of studies have reported that tumor-derived EVs can directly affect cytotoxic function, proliferation and survival of CD8+ CTLs and NK cells (30, 32, 149–157). Early studies showed that EVs carrying Fas ligand (FasL) could induce apoptosis of CD8+ CTLs (149–151, 153, 154), due to their expression of the FasL receptor CD95. TRAIL expressed on tumor exosomes may also contribute to induction of CD8 CTL apoptosis (150). More recently, tumor-derived EVs have been shown to downregulate the activation status of NK and CD8+ T cells by downregulating the receptor NKG2D (152, 155–157). NKG2D is a lectin-like activating receptor that is involved in recognition of transformed and stressed cells and can also activate NK and CTL cytotoxicity, in part by inducing release of cytokines (158, 159). Exosomes from various cancer cell lines or isolated from pleural effusions of mesothelioma patients carry several NKG2D ligands, including MHC class I–related chain (MIC) A (MICA), MICA *008, MICB or UL16-binding proteins 2 (ULBP2), as well as TGFb, which induce downregulation of NKG2D surface levels (155–157). This downregulation appears to affect function, as NKG2D-agonist ab-induced lymphocyte cytotoxicity and secretion of interferon-g was reduced in exosome-treated cells (156). Tumor derived exosomes containing MICA *0008 have also been shown to downregulate “bystander” cell killing by NK cells, presumably still via downregulation of NKG2D with the accompanying reduction of lymphocyte activation (157). In that study, both NKG2D- and non-NKG2D-dependent cell killing were shown to be attenuated by tumor-derived exosome treatment.

Control of Regulatory Immune Cells by EVs

EVs have been shown to regulate additional types of immune cells, including dendritic cells (DCs), regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)(160–171). These cells are critical for orchestrating anticancer cytotoxicity, and dysfunction of these cells is common in cancer (172–174). Although tumor-derived EVs carry tumor antigens to DCs and activate tumor-specific CTLs (163, 164), they can also suppress DC functions. Breast cancer cell-derived exosomes were found to block the maturation of DCs from precursor cells, by delivering IL-6 to activate STAT3 signaling (165). Similarly, tumor-derived EVs were found to interfere with normal differentiation of DCs (166). Monocytes treated with tumor-derived EVs secreted TGFb which suppressed T cell proliferation and cytolytic ability; however detailed mechanisms of this tumor derived MV-mediated phenotypic change are as of yet unknown. Tumor-derived EVs may also regulate function of DCs via activation of Toll-like receptors (TLRs)-Type I interferon (IFN) pathway (167). Downregulation of the Hippo pathway kinases LATS1/2 in tumor cells led to enrichment of nucleic acids in EVs which activated the TLR-Type I IFN pathway in DCs and enhanced secretion of IL-12 to promote cytotoxic activity of CD8+ CTLs.

Tregs control immune responses to foreign antigens including tumor-derived ones, and play a role in preventing tumor rejection (175). Increased frequencies of tumor Tregs correlate with poor prognosis of cancer patients, probably as a consequence of Treg-mediated suppression of antitumor immunity (176). Ovarian cancer- and HNSCC-derived EVs have been shown to induce promote differentiation of CD3+CD4+ T cells into $CD4^{+}CD25^{high}FOXP3^{+}$ Tregs (168). The EVs also promoted expansion and immunosuppressive functions of Treg cells via upregulation of FasL, TGFb, IL-10, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), granzyme B and perforin. In another study, nasopharyngeal carcinoma (NPC)-derived exosomes were similarly found to recruit conventional CD4 T cells and induce their conversion into suppressive Treg cells (161).

Along with Tregs, MDSCs are major immune suppressive cells in the tumor microenvironment (TME) (173). Many studies have reported that tumor-derived EVs promote conversion of monocytes to MDSCs (160, 166, 169–171). The mechanisms include activation of TLR and STAT3 pathways by HSP70 family members expressed on the surface of exosomes. The exosomal HSP70 and HSP72 were shown to interact with TLR2 to promote IL6 secretion and STAT3 phosphorylation (160, 171)

Role of EVs in Immune Checkpoint Control

Recently, immune checkpoint blockade (ICB) has taken on an important role in cancer therapy (177–179). Tumor cells evade killing by immune cells by activating immune checkpoint molecules, which serve to downregulate immune responses via ligand-receptor interactions between T cells, dendritic cells, tumor cells, and macrophages (177, 180). The major and well-studied immune checkpoint molecules are programmed cell death 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), and CTLA-4 (180–182). PD-1 is expressed on activated T cells. Activation of PD-1 by either of its two ligands, PD-L1 and PD-L2, downregulates signaling associated with antigen recognition by the T cell receptor. PD-L2 is

predominantly expressed on antigen-presenting cells (APCs) whereas PD-L1 can be expressed on many cell types, including cancer cells. CTLA-4 is also expressed by activated T-cells and downregulates T-cell function through a variety of mechanisms, including preventing costimulation by CD28 and inducing cell cycle arrest (181, 182). EVs released from chronic lymphocytic leukemia (CLL) cells have been shown to regulate expression of PD-L1 expression in monocytes (183). From the results of RNA sequencing and proteome analyses, noncoding Y RNA hY4 was enriched in exosomes from the plasma of CLL patients compared with healthy donor samples. Transfer of CLL-derived exosomes or hY4 alone to monocytes increased the expression of PD-L1, attenuating tumor immunity to support cancer progression. In other cancers, tumor-derived EVs were shown to increased expression of cytotoxic T lymphocyte antigen 4 (CTLA-4) in Tregs (168), which may enhance Treg activity.

From these studies, some specific immune cell-directed effects of EVs have been identified. However, the immune system is highly complex, and more comprehensive and in-depth studies will be needed to understand the role of EVs in coordinating and controlling anti-tumor immunity.

Conclusions

Many functions of EVs in cancer progression have been identified in the past few years, including roles in promoting cancer invasiveness and metastasis, angiogenesis, and immune regulation. In some cases, molecular mechanisms have been identified; however, by-and-large the role of EV molecular cargoes in various functions remains to be determined. Therefore, a major focus for the future should be on designing clear experiments to definitively test the role of individual or multiple EV cargoes on biological functions. For example, engineered loss or gain of specific cargoes should lead to loss or gain of EV activities in functional assays. Ideally, one should also check whether those perturbations affect additional cargoes in EVs. This is a difficult but important task and must take place before EV therapies targeting specific cargoes can be designed. In addition, many studies focus somewhat arbitrarily on only one class of cargo, e.g. RNA, protein, or lipid, which may limit the scope of investigation and lead to missing important molecular mechanisms. A more broad-based approach may lead to important mechanistic insights. Careful purification and characterization of EVs, such as has been proposed in several publications (184, 185), are also an important component of increasing the rigor and reproducibility of EV experiments and identifying bona fide EV cargoes responsible for biological functions. Finally - although rarely reported to date - it also is the case that sometimes EV secretion from cancer cells may inhibit cancer progression, for example from relatively nonaggressive tumors (133). Understanding which patients to choose for anti-EV therapy, such as drugs that inhibit exosome secretion, should also take such considerations into account. Overall, it is clear that EVs are a major component of the tumor microenvironment that orchestrates the interaction between cancer and host cells to drive cancer progression.

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Summary Points

- Extracellular vesicles (EVs) constitute a major mechanism of cellular communication.
- Tumor-derived EVs play important roles in multiple steps of cancer progression, including cancer invasiveness and metastasis, angiogenesis, and immune regulation.
- In the process of cancer progression, tumor-derived EVs can act in both an autocrine and paracrine manner.
- The role of EV molecular cargoes in various functions is still poorly defined and is an important area of future investigation.

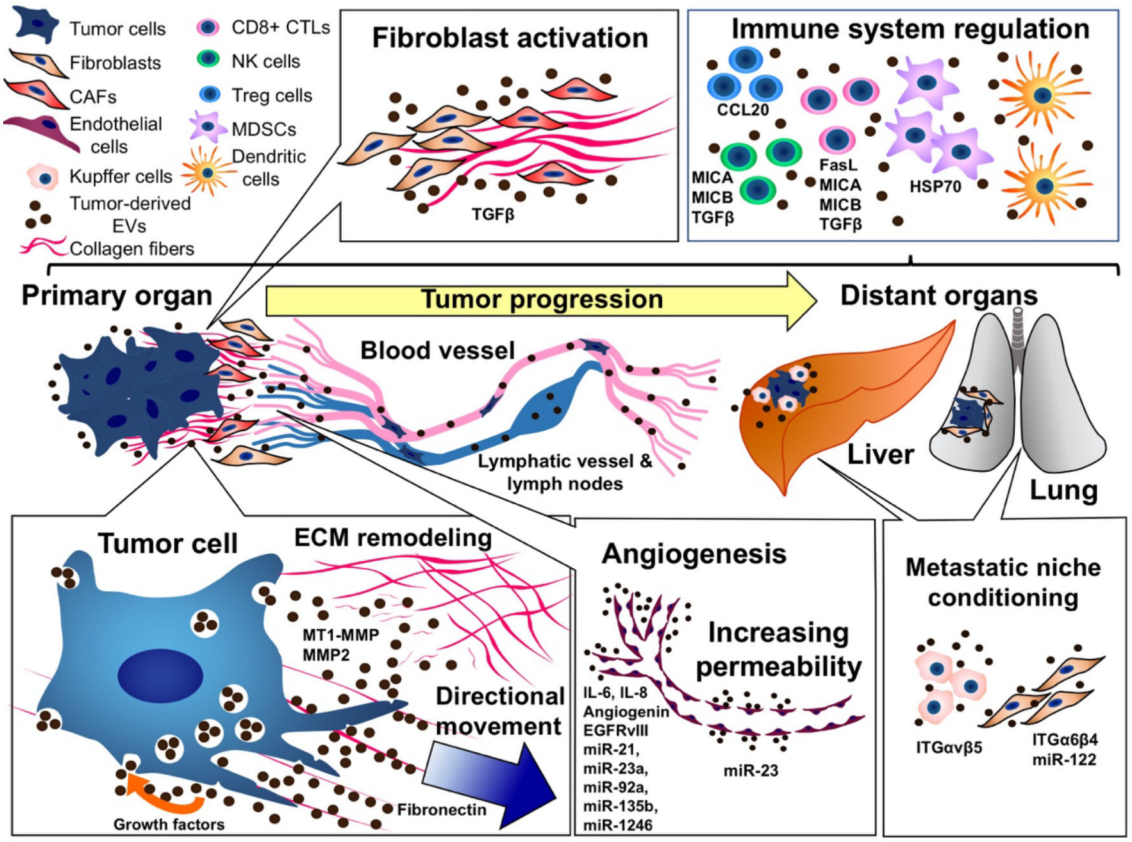

Figure 1. The role of extracellular vesicles (EVs) in tumor progression.

Tumor cell-derived EVs mediate both paracrine and autocrine communication. At the primary lesion, tumor-derived EVs facilitate autocrine mechanisms of growth, migration and invasion via growth factor, ECM and proteinase cargoes. Paracrine communication via cancer-derived EVs promotes transformation of fibroblasts into cancer-associated fibroblasts (CAFs) that can also promote cancer invasiveness via remodeling of ECM. Tumor-derived EVs also facilitate angiogenesis and promote vascular permeability, which may promote intravasation of tumor cells. Tumor-derived EVs can reach distant organs and affect organ-specific stromal cells, such as Kupffer cells in the liver or fibroblasts in the lung, to promote pre-metastatic niche formation. Tumor immunity can also be influenced by cancer-derived EVs, including attenuation of cytotoxic function of CD8+ CTLs and NK cells, and increased activity of Treg cells and MDSCs. EV molecular cargoes shown in the figure are from references (46, 47, 66, 92–94, 105, 109, 111, 112, 125, 127, 151–157, 160, 161, 171).