The Role of Exosomes in Tumor Microenvironment Remodeling and Cancer Metastasis: A Review

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Abstract
Molecular changes within the cancer cells are not enough to explain the metastatic potential of malignant tumors. The communication between the malignant cells and their cellular and extracellular milieu is crucial for the progression of the tumor. The mediators that participate in this communication have received a lot of attention in recent years, not only for the biological activity they carry but also because of their ability to trans-fer biologically active material from one cell population to the other, notably exosomes and other small extracellular vesicles. These vesicles can carry proteins, lipids, messenger RNAs, microRNAs, long non-coding RNAs, circular RNAs, enzymes and other signalling molecules that can aid in changing the phenotype of the recipient cells. In the tumor microenvironment, exosome mediated signalling can activate fibroblasts, induce metabolic adaptation, induce angiogenesis, cause endothelial dysfunction, immune escape, epithelial–mesenchymal plasticity and extracellular matrix remodeling. Their impact is not confined to the primary tumor, as tumour-derived vesicles in circulation can also modulate distant tissues, and aid in the formation of pre-metastatic niches before metastasis can occur. Exosomes have also been shown to be secreted by stromal cells, such as cancer associated fibroblasts and macrophages, which can further promote tumor cell migration, invasion and therapy resistance. These biological characteristics have led to their exploration as liquid-biopsy markers and as therapeutic targets and/or delivery systems. Although significant advances have been made, there are also important challenges, including vesicle heterogeneity, reproducibility, large-scale production methods, and extracellular-vesicle classification and isolation methods, as well as clinical validation. The current review explores the key pathways through which exosomes are involved in remodeling the tumor microenvironment and promoting metastasis, focusing on stromal reprogramming, vascular alterations, immune modulation, EMT and ECM alterations, and pre-metastasis niche formation. Current applications in diagnosis and treatment, methodological shortcomings and future research priorities are also critically examined.

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1. Introduction

Spread of cancer to other parts of the body is still one of the most significant biological characteristics of cancer that contributes to cancer deaths. Metastasis involves a series of coordinated steps, including the release of the tumour cells from the primary site, invasion of the adjacent tissue, entry of the malignant cells into blood vessels or lymphatics, survival in the blood or lymph, entry into other tissue and successful metastasis. Genetic and epigenetic changes in the cancer cells are key to these events, but

the ability of a metastasis to succeed also relies heavily on interactions with neighbouring non-cancerous cells and extracellular structures [2, 4].

The tumor microenvironment (TME) is now considered as a more active player in cancer progression than a passive background. It has fibroblasts, endothelial cells, macrophages, lymphocytes, neutrophils, myeloid-derived suppressor cells, extracellular matrix components, soluble cytokines, chemokines, growth factors and extracellular vesicles. Interactions between these elements may alter the phenotype of the tumour cells and influence the nature of the tumour – localized or more invasive and metastatic.

One of the key ways in which this communication is now known to take place involves extracellular vesicles. The exosomes are particularly being studied because they are able to transport complex molecules and shield them from extracellular destruction. Exosomes were originally described as small membrane-bound vesicles derived from the endosomal pathway and secreted from cells after endosomal fusion with the plasma membrane. However, the current guidelines for extracellular-vesicles suggest caution in the use of the word “exosome” without experimental evidence of an endosomal origin [1]. The term “small extracellular vesicles” might thus be a more appropriate scientific term in many studies.

Although this distinction exists, the word exosome is still used in the cancer literature and will be used throughout this review when referring to studies that used this word.

Membrane proteins, signaling molecules, lipids, enzymes, messenger RNA, microRNAs, long non-coding RNAs, circular RNAs, and fragments of DNA are among the molecular components of exosomes [1, 4]. When delivered to recipient cells, these molecules can change the expression of genes, signal transduction, metabolism, immune activity, cell migration and cell survival. Thus, exosomes could have a significant impact on the non-cancerous and cancerous components of the TME.

Importantly, the communication via EVs is not limited to the interaction of tumor cells with neighbouring cells. There are also vesicles secreted by stromal cells that can modify the behavior of cancer cells. Cancer-associated fibroblasts, macrophages, and endothelial cells could then be involved in a series of functional interactions that gradually create a more conducive tumor microenvironment.

Exosomes can also act outside of the primary tumor. Vesicles in the circulation can interact with tissues at distant sites, modify endothelial barrier function, activate resident stromal cells, recruit bone marrow derived cells, or modify extracellular matrix composition. In the context of pre-metastatic niche (PMN) formation, such systemic regulation is increasingly thought to be relevant [4, 7, 8].

Extracellular vesicles at the translational level have been of interest as a potential source of biomarkers, as the molecular content of these vesicles can be found in blood and other body fluids. At the same time, engineered exosomes have been also studied as a carrier for RNA molecules, drugs, and other therapeutic molecules [23, 29].

In this review, we summarize and critically evaluate the current evidence showing the participation of exosomes in the remodeling of the TME and in the promotion of metastasis. A particular focus is placed on tumor–stroma interactions, angiogenesis, immune modulation, EMT-associated plasticity, extracellular matrix remodeling, pre-metastatic niche formation, biomarker development, and novel therapeutic implications.

2. Exosome Biogenesis, Molecular Cargo, and Cellular Communication

The process of exosome formation starts in the endosomal system. Early endosomes are formed after internalization of parts of the plasma membrane, which then develop into late endosomal compartments. When the endosomal limiting membrane buds outwards, small vesicles are formed within the endosome, creating multivesicular bodies. There are then two major pathways that these structures can be directed: fusion with lysosomes where their contents are degraded, or fusion with the plasma membrane leading to the release of intraluminal vesicles into the extracellular environment [1, 4].

There are a number of molecular systems that regulate this process. Endosomal sorting complexes (ESC) involved in transport play a role in membrane remodeling and in the generation of intraluminal vesicles (ILVs). There are also alternative mechanisms other than ESCRTS, such as ceramide, tetraspanins and specialized membrane microdomains. Rab-family GTPases and related trafficking proteins are involved in the transport, docking and discharge of vesicle-enclosed compartments [1].

The cargo content of exosomes can vary greatly. Structural proteins, heat-shock proteins, adhesion molecules, enzymes, receptors, lipids and several kinds of nucleic acids can be found in vesicles. They are dependent on the physiological or pathological status of the cell they originate from and the cell's phenotypic state.

This is especially true in cancer, where the malignant cells are often under hypoxic, nutrient stress, inflammatory influence, and anticancer treatment conditions. Environmental stresses can affect the amount of EVs released and the contents of the EVs [2, 4].

Not all cargo is incorporated in a random fashion. Some proteins and RNA molecules can be selectively concentrated in vesicles, making it possible for cancer cells to selectively release messages that affect certain target populations.

Once secreted, extracellular vesicles can interact with recipient cells in a variety of ways. Some vesicles can enter cells by endocytosis, phagocytosis, macropinocytosis, and/or direct membrane fusion, while others can trigger signaling upon binding to surface receptors without entering. The cargo, once available to the recipient cell, could alter transcription, levels of proteins, metabolism, or signaling networks.

The resulting biological impacts are very context-dependent. The vesicles produced by the various tumor-cell clones can vary greatly in their activities. Similarly, immune and stromal cells can release vesicles that can either drive or inhibit malignant progression, depending on their source, content and specific cellular context.

Exosomes should not be considered a homogeneous population of molecules, for this reason. Their diversity is an important aspect of their biology as well as a benefit and a challenge for therapeutic development.

3. Exosomes as Components of the Tumor Microenvironment

Tumor microenvironment is an ever-evolving ecosystem in which both malignant and non-malignant cells interact with each other. The biological behavior of a tumor is influenced by several types of cells, including fibroblasts, endothelial cells, immune cells, mesenchymal cells, extracellular matrix

proteins, soluble mediators and extracellular vesicles.
Signals can be exchanged between these populations without direct cell-to-cell contact, via exosomes [2, 4]. Vesicles can be secreted by cancer cells that change the activity of fibroblasts, the behaviour of endothelial cells, the phenotype of macrophages, the function of lymphocytes and the composition of extracellular matrix.
This communication can be two-way. Upon reprogramming by tumor-derived exosomes, stromal cells could also secrete their own exovesicles which could then act back on the malignant cells. These secondary signals may promote proliferation, motility, invasion, metabolic flexibility and treatment resistance.
These mutually interdependent relationships can form self-reinforcing signaling loops. For instance, activated fibroblasts release extracellular vesicles, cytokines and matrix components, that promote tumor aggressiveness, while malignant cells, in turn, stimulate fibroblast activation. The extracellular-vesicle signaling is also coupled to the traditional soluble signaling mechanisms. Exosomal communication can occur in parallel with cytokines, chemokines, growth factors and extracellular matrix derived signals.
Therefore, exosomes in cancer biology should be viewed as part of a larger intercellular communication network that works together to influence the progression of cancer.

4. Exosome-Driven Remodeling of the Tumor Microenvironment

Among the most important stromal cells that play a role in tumor progression are the cancer-associated fibroblasts (CAFs). They play a role in extracellular matrix deposition, angiogenesis, inflammation, immune suppression, metabolic support, and therapeutic resistance. This is one way in which fibroblasts gain these tumor supportive properties, via exosomal communication.
A tumor-derived exosomal HSPC111 was found to modify stromal lipid metabolism and promote the progression of colorectal cancer metastasis to the liver [11]. The study showed that exosomal transfer of HSPC111 modulated ATP-citrate lyase-related metabolic pathway in fibroblasts and enhanced the secretion of CXCL5, which may be used to demonstrate that vesicles can alter the biochemical status of the metastatic microenvironment.
In hepatocellular carcinoma, another pathway has been demonstrated. It has been reported that the exosomal miR-1247-3p that was released from highly metastatic tumor cells was transferred to fibroblasts and suppressed B4GALT3 expression, while promoting the activation of β1-integrin/NF-κB signaling [12]. This phenotype of the fibroblasts correlated with the creation of a pro-inflammatory environment, which promotes lung metastasis.
The interaction between cancer cells and fibroblasts is two-way. The stromal cells may also produce exosomes that can directly promote the behaviour of the malignant cells. Luga *et al*. have shown that the migration of breast cancer cells is enhanced by fibroblast-derived exosomes via Wnt-planar cell polarity signaling [13].
Circ_0067557 was found to facilitate the proliferation, metastatic ability, and chemoresistance in colorectal cancer through the Lin28 proteins within vesicles derived from CAFs [15].
These interactions can be further enhanced when hypoxia (low oxygen levels) occurs. In prostate cancer, exosomal miR-500a-3p from the CAFs was shown to regulate the FBXW7/HSF1 signaling axis and to enhance the metastatic capacity under hypoxic conditions [14].
The above results suggest that the exosomes act by several parallel mechanisms in the remodeling of the TME. They have the ability to alter stromal-cell differentiation, metabolism, inflammatory signaling, transcription regulation, and the communication between tumor and stroma.

5. Contribution of Exosomes to Metastatic Progression

Cancer cells need to constantly adapt to new conditions when they move to different tissues. A cell that is able to escape from a primary tumor will have to invade the surrounding tissues, enter the circulation, withstand mechanical and immune pressure, exit the circulation, and survive in a new tissue.
At various stages, exosomal signaling can help to facilitate several of these processes [3, 4].
One of the first influential studies in this field was reported by Peinado *et al*., who indicated that melanomas could remodel bone-marrow progenitor cells, inducing a pro-metastatic phenotype that is dependent on MET signaling [5]. This study significantly advanced the concept that cancer-derived vesicles could lay the foundation for the systemic environment in the spread of metastases.
Some of the observations, however, have been subsequently investigated for reproducibility. Kim *et al*. replicated some of the original experimental design to find some of the results were less dramatic and some comparisons of metastatic burden did not reach significance [6].
This discovery is significant as it reveals a wider problem in the field of extracellular vesicles. It is important to note that the biological effects that have been attributed to exosomes can be dependent on the method of vesicle isolation, the dose, route of administration, cell line properties, animal models, and sample size.
However, there is emerging evidence from independent studies to suggest that the process of extracellular-vesicle-mediated signaling can promote metastasis in at least several ways. Exosomes derived from the fibroblasts can promote the movement of tumour cells [13]; vesicles from macrophages can promote invasion [18]; and vesicles from cancer cells can modulate vascular permeability and metastatic niche formation [8, 10].
Exosomes are, therefore, not likely to act via a common, universal metastatic pathway. Their contribution is instead spread over a number of biological processes that all contribute to tumor dissemination.

6. Exosomes in the Establishment of Pre-Metastatic Niches

The pre-metastatic niche is an idea that distant organs can undergo biological changes before metastatic cancer cells arrive. Selected tissues can be changed so that they are more favorable for subsequent colonization.
One mechanism by which the primary tumors may affect these distant environments is believed to be through extracellular vesicles.
In the case of pancreatic ductal adenocarcinoma, a remarkable progress was reported. Pancreatic cancer derived exosomes were shown by Costa-Silva *et al*., to induce changes within the liver prior to the establishment of overt metastatic colonization [7]. The Kupffer cells were found to

be involved in the uptake of tumor vesicles, and this process was correlated with transforming growth factor-β signaling, activation of hepatic stellate cells, deposition of fibronectin, and recruitment of bone-marrow-derived cells. Macrophage migration inhibitory factor, a factor identified as being important in this process, was found in exosomes.

For example, colorectal cancer. The ability to modify the pathways regulated by KLF2 and KLF4 in endothelial cells through interaction with exosomal miR-25-3p led to a rise in vascular permeability and angiogenic activity [8]. These vascular effects stimulated conditions conducive to metastatic dispersion.

Further, exosomal ADAM17 has been shown to be involved in colorectal cancer. The vesicles secreted by tumors containing ADAM17 altered the organization of vascular endothelial cadherins and caused an increase in vascular permeability, which aids in the development of the pre-metastatic niche [10].

Distant stromal fibroblasts can also be altered by exosomes derived by the tumor. In HCC cells, miR-1247-3p-containing vesicles induced B4GALT3/β1-integrin/NF-κB-related signaling to recruit fibroblasts for the development of lung metastasis [12].

Further contributing to this process is hypoxia. Small extracellular vesicles (sEVs) containing hypoxia-associated LOXL2 were demonstrated to affect both the malignant cells and the fibroblasts in head and neck squamous cell carcinoma (HNSCC). These vesicles improved EMT features and promoted fibronectin production via FAK/Src pathway [21].

The results suggest that the development of a pre-metastatic niche requires more than one molecular event. Instead, it is characterized by coordinated changes in endothelial integrity, extracellular matrix organization, stromal activation, inflammation, metabolism and immune-cell recruitment.

Recent studies of the field still favor the role of tumor-derived EVs, but the studies are still diverse and physiologically more representative models are needed [30, 31].

7. Bidirectional Exosomal Communication Between Tumor and Stromal Cells

Communication occurs between the cancer cells and the stromal cells, bi-directionally. This interaction of malignant cells and fibroblasts is especially pronounced.

Extracellular vesicles that target the migration and signalling of tumour cells can be generated by fibroblasts. Luga *et al*. demonstrated that Wnt-planar cell polarity signaling was involved in the fibroblast-generated CD81+ exosomes stimulating breast cancer-cell protrusive behavior and migration [13].

In CRC, the exosomes derived from CAFs promoted the growth, migration, invasion and chemoresistance of malignant cells by signaling through Lin28 [15].

Exosomes also play a role in stromal communication, which is also mediated by macrophages. Lan *et al*. showed that miR-21-5p and miR-155-5p were transported into CRC cells by vesicles from M2 macrophages [18]. These miRNAs suppressed the expression of BRG1 and promoted migration and invasion.

The observations suggest that stromal cells are not mere responders to the tumor signals. They can switch to being active producers of extracellular vesicles that promote malignant phenotypes when changed by the tumour environment.

The resulting two-way interaction can result in positive-feedback loops that allow the cancer cells and stromal populations to mutually support each other.

Therapeutically, interference with these signaling loops is desirable because one single intervention could potentially interfere with multiple downstream processes. It's difficult, though, to achieve specificity, due to the fact that the production and uptake of extracellular-vesicles are also key parts of normal physiology.

8. Exosomes, Angiogenesis, and Endothelial Dysfunction

There is close association between tumor growth and vascular remodeling and their metastatic spread. Tumor vessels are newly formed vessels that deliver nutrients and oxygen to the tumors but are frequently structurally abnormal and have high permeability. Communication by exosomes can lead to both angiogenesis and endothelial barrier dysfunction.

The role of exosomal miR-25-3p in colorectal cancer (CRC) was demonstrated to regulate endothelial-cell signaling via KLF2 and KLF4 [8]. The effect was linked to increased angiogenesis and alteration of endothelial-junction proteins, facilitating the permeability of the blood vessels.

A similar phenomenon has been described in non-small-cell lung cancer. Exosomal miR-3157-3p derived from tumors was transferred to endothelial cells and affected the pathways of TIMP, KLF2, VEGF, MMP2, MMP9 and occludin [9]. The changes brought about enhanced the angiogenic activity and endothelial permeability.

Exosomal ADAM17 is a protein-based mechanism. In the colorectal cancer model, vesicular ADAM17 was found to change the organization of VE-cadherin in endothelial cells, which led to loss of vascular integrity [10].

The results indicate that vesicles derived from tumours can influence the vascular system in several ways. They can promote the development of new blood vessels, disrupt intercellular junctions, and make the blood vessels permeable to tumor cells entering the bloodstream and leaving to go to the metastatic site.

Therefore, exosome-mediated vascular remodeling is an important biological link between the local expansion of tumor and its distant spread.

9. Exosome-Mediated Immune Modulation and Tumor Immune Escape

In addition to the ability to invade, cancer cells must also be able to avoid immune surveillance for cancer to progress. Extracellular vesicles play a role in this process via the transfer of immunoregulatory proteins and nucleic acids to immune cells.

One of the best-known is programmed death-ligand 1 (PD-L1). To demonstrate, Chen *et al*. showed that melanoma cells can excrete functional PD-L1 containing exosomes [16]. These vesicles were found to be responsible for systemic suppression of antitumor immunity and linked to anti-PD-1 response.

Poggio *et al*. then demonstrated that an exosomal PD-L1 immunotherapic intervention increased the systemic anti-tumor immune responses and induced immune memory in an experimental setting [17].

Exosomes have other ways to impact immunity. They can affect macrophage polarization, T-cell activation, function of dendritic-cells, natural-killer-cell activity, and behaviour of MDC, depending on their source and molecular content [28, 32].

The connection between immune modulation and metastasis is prominent. For instance, M2 macrophages can generate vesicles directly promoting the invasion of tumor cells. Lan *et al*. reported that the exosomes derived from M2 macrophages could inhibit the expression of BRG1 and enhance the migration and invasion efficiency of colorectal cancer cells by regulating miR-21-5p and miR-155-5p [18].

Hence, exosomal immune regulation should not be considered merely as the inhibition of the activity of lymphocytes. It also encompasses indirect effects whereby immune cells that are changed by the TME then send pro-metastatic signals back to the malignant cells.

The implications for clinical practice are large. Exosomal PD-L1 and other immune-related cargo may be used as treatment response biomarkers, and disruption of these immunosuppressive vesicle pathways selectively may potentially improve current immunotherapies.

These options are presently under further investigation with well-designed prospective clinical studies, however.

10. Exosomes in Epithelial–Mesenchymal Plasticity and Tumor-Cell Migration

The process of epithelial-mesenchymal transition is a phenomenon in which epithelial cells gain characteristics of increased motility, loss of intercellular adhesion and a more invasive phenotype. In cancer, this process can be dynamic and reversible and is referred to as the epithelial–mesenchymal plasticity.

This phenotypic transition can be regulated by exosomes via multiple molecular mechanisms.

Liu *et al*. [19] found that tumor derived-exosomal miR-106b-3p induced migration, invasion, EMT like changes, and lung metastasis in CRC by activating migration and invasion genes by targeting DLC-1. It is important to note that circulating exosomal miR-106b-3p was also elevated in patients with metastatic disease, thus highlighting a direct link between the mechanism and clinical relevance.

Similar effects may occur with stromal vesicles. In oral squamous cell carcinoma, the exosomal miR-34a-5p from CAF has been found to control the AXL-related signaling and downstream AKT/GSK-3β/β-catenin/Snail pathways [20]. The increases in malignant progression were related to these changes.

Tumors can also produce vesicles that have the ability to stimulate the expression of mesenchymal properties in hypoxic tumor cells. Small EVs derived from hypoxic HNCs enriched in LOXL2 enhanced the EMT-like phenotype and invasion in target cells [21].

Macrophages derived vesicles can also strengthen cell migration and invasion, such as miR-21-5p and miR-155-5p that are transferred from M2 macrophages to colorectal cancer cells [18].

Overall, the data indicate that exosomes are involved in various different pathways that act on the epithelial–mesenchymal plasticity, but with overlap. Their effects are tissue and cell dependent, and depend on the environmental conditions, their molecular cargo, and the type of tumor.

11. Exosomes in Extracellular Matrix Remodeling and Tumor Invasion

The extracellular matrix is more than just a mechanical scaffold. It is actively involved in controlling cell adhesion, cell migration, cell differentiation and cell signaling. As the tumor grows, significant matrix remodeling is necessary to allow the local invasion and spread of tumour cells to distant tissues.

Exosomes can affect this process both by modifying the stromal cells that produce the matrix, and by carrying molecules, which can directly affect matrix degradation.

In the pancreatic cancer study by Costa-Silva *et al*., it was shown that tumor-derived vesicles were correlated with an increase in the deposition of fibronectin in the liver during the formation of the pre-metastatic niche [7].

A similar mechanism has been reported for small extracellular vesicles (sEVs) containing LOXL2. In head and neck cancer, these vesicles activated fibroblasts and induced fibronectin production by FAK/Src-dependent signaling [21].

In addition to the indirect participation in the degradation of the matrix, exosomes may be directly involved in it. Palmulli *et al*. reported that MT1-MMP is found on the membrane-bound exosomes which remain near the surface of breast cancer cells [22]. The localization of these protease containing vesicles promoted degradation of the extracellular matrix and helped the tumor cells to invade.

Exosomal signaling also may affect expression of matrix metalloproteinases (MMPs) including MMP2 and MMP9. Vesicle-mediated pathways have been associated with these enzymes in lung and oral cancers [9], [20].

Based on this, exosomes may play a role in the extracellular matrix remodeling in two complementary ways: modifying the activity of matrix-producing stromal cells and delivering and/or modulating the activity of matrix-degrading proteases. These processes are involved in primary-tumor invasion and in the establishment of microenvironments for metastatic colonization.

12. Exosomes as Diagnostic and Prognostic Biomarkers

The molecular cargo of EVs is a reflection, at least in part, of the biological state of the cells that produce them. Vesicles are attractive candidates for liquid-biopsy applications, as they are capable of being found in the circulation, e.g., in blood and other bodily fluids.

Applications in the clinic involve early detection of cancer, cancer classification, evaluation of metastatic potential, prediction of response to treatment, detection of residual disease, monitoring for recurrence, and others [23]_[26].

Exosomal protein, miRNA, mRNA, DNA fragments, and lipid signatures have all been examined as potential exosomal biomarker.

There are also several mechanistic studies mentioned above that support the biomarker potential. A high level of exosomal miR-3157-3p was observed in metastatic NSCLC [9]. Exosomal ADAM17 was found to be a possible marker for colorectal cancer metastatic progression [10]. In CRC, the expression level of exosomal miR-106b-3p was linked to metastasis and poor prognosis [19]. It was found that LOXL2 in small EVs in the circulation was linked with aggressive features of head and neck cancer [21]. Additionally, the expression of PD-L1 in exosomes has been studied in the context of response to immunotherapy [16].

A major potential avenue is the use of multiple analytical chemicals or “signatures” in place of a single biomarker. A combination of multiple vesicle-associated proteins, RNAs, lipids or metabolites could enhance the diagnostic and prognostic value [24].

But there are significant methodological shortcomings. The different isolation protocols yield different populations of extracellular vesicles. The differences in recovery and purity

of the methods include ultracentrifugation, size-exclusion chromatography, polymer precipitation, filtration, immunoaffinity methods, and microfluidic technologies [1], [25].

Results may also be affected by pre-analytical conditions. EV-based measurements are vulnerable to sample collection, anticoagulant type, processing delay, plasma lipoproteins and freeze–thaw cycles, contamination [1, 25].

The results in exploratory cohorts should not be interpreted as being the same as validated clinical biomarkers for this reason.

There is a need for standardised protocols, independent external validation, prospective patient cohorts, comparison with existing clinical guidelines and evidence that exosome-based testing enhances clinical decisions making to ensure reliable clinical translation.

13. Therapeutic Targeting and Clinical Applications

The role of EVs in cancer has sparked two parallel therapeutic strategies. The former inhibits the tumor-derived vesicles from sending signals to kill the tumor, while the latter looks to use the vesicles as delivery agents.

13.1. Reducing Tumor-Derived Vesicle Production

Blocking the extracelluar-vesicle biogenesis or release could decrease communication between the malignant cells and the supportive stromal cells. Molecules of potential interest are those involved in endosomal trafficking, ceramide metabolism, Rab-family signaling and membrane-fusion mechanisms. One major drawback of this approach is that normal extracellular-vesicle biology might be disrupted. Broad inhibition may result in systemic effects as vesicles are used throughout the body in physiological communication.

13.2. Preventing Uptake by Recipient Cells

The blocking of tumor-derived vesicles from being taken up by endothelial cells, fibroblasts, macrophages or cells in distant organs may theoretically decrease TME remodeling and pre-metastatic niche formation.

However, there are several pathways by which extracellular-vesicles can be internalized, such as endocytosis, receptor-mediated uptake, membrane fusion and macropinocytosis.

Due to this complexity, it is difficult to develop a selective inhibitor that blocks the production of vesicles derived from tumors without affecting the communication between cells in the body.

13.3. Targeting Specific Exosomal Cargo

A more selective approach is to target molecular cargo which causes harmful biological effects.

One such marker is the exosomal PD-L1. Experimental blockade of PD-L1-positive vesicles boosted anti-tumor immunity in a preclinical model [17].

Other options include the proteins of stromal or endothelial reprogramming, ADAM17, LOXL2, metastasis-associated miRNAs [10, 19, 21].

This might be more specific than general suppression of the production of extracellular-vesicles.

13.4. Exosomes as Therapeutic Delivery Vehicles

Engineering of EVs for therapeutic delivery is another approach to oppose their inhibition.

They have the natural membrane structure and the ability to protect the cargo, and they can penetrate the recipient cells which make them useful for transporting RNA molecules, proteins, or drugs [26, 27, 29].

Kamerkar *et al*. reported an important proof of concept study in which they modified exosomes with RNA-based therapeutics to target oncogenic KRASG12D in models of pancreatic cancer [27]. Treatment decreased KRAS-induced signaling and prevented the growth of tumors in experimental models.

The cargo for engineered exosomes can include siRNA, miRNA mimics, antisense molecules, mRNA, proteins, chemotherapeutic agents, immune-modulating compounds, and genome-editing components.

It is also possible the surface modification will be used to target delivery to certain tissues or tumor types.

Clinical development is technically challenging, however, these benefits make it worth the effort. Methods of production should produce uniform vesicles that can be loaded with consistent cargo, be free from contamination, remain biologically active, and remain stable.

Other issues are biodistribution, immune effects, unintended affinity to healthy tissues, storage, batch-to-batch variation, and regulatory categorization.

Hence, engineered exosome therapy is still a platform that cannot be used routinely yet for cancer treatment.

14. Challenges and Limitations of Current Exosome Research

The field of extracellular-vesicles has grown significantly, but there are a few challenges in interpreting the published data.

The first problem has to do with the terminology. The presence of a particle in the presence of commonly used vesicle markers is not proof that it is from the endosomal pathway. For this reason, MISEV2023 suggests caution in reporting and strongly discourages the use of language specific to biogenesis unless proven to be the origin [1].

Secondly, there is the issue of isolation. Variations in purification technique yield populations of vesicles varying in purity and can co-isolate proteins, lipoproteins, or other nanoparticles.

Third, EVs are in themselves heterogeneous. Genetically similar tumor cells can shed vesicles with various contents, depending on the oxygen level, the nutrient condition, the therapy received, and the stress on the cells.

Fourth, experimental models, like physiology, do not always mimic physiological conditions. The majority of studies expose cells and/or animals to purified extracellular vesicles at concentrations that are likely to be higher than those normally found in patients.

The experiment on melanoma exosomes is an instructive example of replication studies. The systemic effects were reported to be strong in the original report, but later reports yielded less clear results for some endpoints [5] [6].

This does not rule out the whole concept of extracellular-vesicle biology but emphasizes the importance of strict controls and independent confirmation.

Another challenge is the distinction of the effect of exosomes from the effects of other types of intercellular communication (soluble cytokines, growth factors, circulating tumor cells, matrix fragments).

More issues exist with Biomarker research. Various studies have been conducted with rather small sample sizes, with no independent confirmation, and with different sample processing methods [24, 25].

The manufacturing and quality assurance of therapeutic applications pose additional problems of reproducibility, potency testing, toxicology, biodistribution and regulatory control [26, 29].

When interpreting the implications of these statements about the diagnostic or therapeutic potential of exosome-based technologies, the following limitations should be taken into account:

15. Future Perspectives

There are several regions that have the potential to influence the future of extracellular-vesicle research in oncology. Single-vesicle technologies are of special interest because the bulk measurements usually consist of very heterogeneous populations. Vesicle-specific characterization at the level of individual vesicles may aid in the identification of tumor-specific subpopulations and the separation from vesicles derived from normal tissues. The other multi-omics approaches are significant as well. Combining the RNA profile contained in exosomes with the protein, lipid and metabolome data will provide more comprehensive biological signatures than any single measurements alone [23] and [24]. An additional objective is to pinpoint the precise route taken followed by the vesicles as they travel between the cells in intact tumors. The ability to use spatial biology and single cell technologies together could help researchers identify cell populations that shed specific EV sub-classes and those that are targeted. Longitudinal studies of humans will be especially useful in the research of metastasis. If changes to the cargo of extracellular vesicles do predate metastatic progression, then sampling patients before and during metastasis formation could help answer this question.

The preclinical models should also be more physiologically relevant. Recent reviews have focused on the use of exogenously administered isolated vesicles, rather than on the direct observation of vesicles that are naturally released from growing tumors [31]. Therapies of the future are also expected to be more targeted. Interventions need not be general inhibitors of extracellular-vesicle synthesis, but instead could target surface proteins, cargo associated with disease, or uptake pathways. To fully benefit from engineered exosome technology, scaling up the manufacturing process, loading of cargo, quality control, storage, targeting efficiency, pharmacokinetics, and safety over longer periods of time will need improvement [26, 29]. Last but not least, methodological standardization is needed. The international recommendations (MISEV2023), reporting of isolation and characterization procedures, independent replication and external clinical validation will improve the reproducibility of the field [1].

16. Conclusion

Recently, a role of small extracellular vesicles, known as exosomes, has emerged in cancer progression and has entered into the current models. They can carry functional molecular payloads and can modify fibroblasts, endothelial cells, immune populations, the extracellular matrix structure, and distant tissue. This vesicle-mediated communication plays a role in several metastasis-related processes, such as stromal activation, angiogenesis, endothelial–barrier disruption, immune suppression, epithelial–mesenchymal plasticity, matrix remodeling, and pre-metastatic niche formation. The communication network is also bidirectional. The vesicles released from stromal cells modified by the tumor can then have a second impact on these cells, promoting their migration, invasion, metabolic adjustment, and therapeutic resistance. The discovery that tumor EVs can alter distant organs before metastatic cells reach them has furthered the understanding of how the primary tumor can prepare the secondary organs for colonization. Exosomes are also highly translational. The molecular constituents may be able to yield liquid-biopsy markers for diagnosis, prognosis, and monitoring of treatment and engineered vesicles could be used as vehicles for therapeutic cargo. But there are still significant hurdles in the way of the field. Currently, the use of EV is limited in clinical routine due to the lack of reproducibility, limited number of experimental models, heterogeneity of EVs, inconsistent naming conventions, and lack of prospective validation. The future course of action will rely on strict experimental design, standardized methodology, mechanistic validation, single-vesicle and multi-omic technologies, long term clinical studies, and reproducible production of therapeutic vesicles. In addition to facilitating a better understanding of metastatic biology, the developments could also lead to strategies for the identification, monitoring, prevention and treatment of metastatic cancer.

References

1. Welsh JA, *et al*. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. J Extracell Vesicles. 2024;13(2):e12404. doi:10.1002/jev2.12404.
2. Chen S, Sun J, Zhou H, Lei H, Zang D, Chen J. New roles of tumor-derived exosomes in tumor microenvironment. Chin J Cancer Res. 2024;36(2):151-166. doi:10.21147/j.issn.1000-9604.2024.02.05.
3. Panda SS, Sahoo RK, Patra SK, Biswal S, Biswal BK. Molecular insights to therapeutic in cancer: role of exosomes in tumor microenvironment, metastatic progression and drug resistance. Drug Discov Today. 2024;29(8):104061. doi:10.1016/j.drudis.2024.104061.
4. Zhang C, *et al*. Tumor-derived small extracellular vesicles in cancer invasion and metastasis: molecular mechanisms, and clinical significance. Mol Cancer. 2024;23:18. doi:10.1186/s12943-024-01932-0.
5. Peinado H, *et al*. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat Med. 2012;18(6):883-891. doi:10.1038/nm.2753.
6. Kim J, *et al*. Replication study: melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Elife. 2018;7:e39944. doi:10.7554/eLife.39944.
7. Costa-Silva B, *et al*. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol. 2015;17(6):816-826. doi:10.1038/ncb3169.
8. Zeng Z, *et al*. Cancer-derived exosomal miR-25-3p promotes pre-metastatic niche formation by inducing vascular permeability and angiogenesis. Nat Commun. 2018;9:5395. doi:10.1038/s41467-018-07810-w.
9. Ma Z, *et al*. Tumor-derived exosomal miR-3157-3p promotes angiogenesis, vascular permeability and metastasis by targeting TIMP/KLF2 in non-small cell lung cancer. Cell Death Dis. 2021;12:840. doi:10.1038/s41419-021-04037-4.
10. Li K, *et al*. Tumor-derived exosomal ADAM17 promotes pre-metastatic niche formation by enhancing

vascular permeability in colorectal cancer. J Exp Clin Cancer Res. 2024;43:59. doi:10.1186/s13046-024-02991-3.
11. Zhang C, *et al*. Cancer-derived exosomal HSPC111 promotes colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts. Cell Death Dis. 2022;13:57. doi:10.1038/s41419-022-04506-4.
12. Fang T, *et al*. Tumor-derived exosomal miR-1247-3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer. Nat Commun. 2018;9:191. doi:10.1038/s41467-017-02583-0.
13. Luga V, *et al*. Exosomes mediate stromal mobilization of autocrine Wnt-PCP signaling in breast cancer cell migration. Cell. 2012;151(7):1542-1556. doi:10.1016/j.cell.2012.11.024.
14. Liu Z, *et al*. Cancer-associated fibroblast exosomes promote prostate cancer metastasis through miR-500a-3p/FBXW7/HSF1 axis under hypoxic microenvironment. Cancer Gene Ther. 2024;31(5):698-709. doi:10.1038/s41417-024-00742-2.
15. Yang C, *et al*. Exosomes derived from cancer-associated fibroblasts promote tumorigenesis, metastasis and chemoresistance of colorectal cancer by upregulating circ_0067557 to target Lin28. BMC Cancer. 2024;24:64. doi:10.1186/s12885-023-11791-5.
16. Chen G, *et al*. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature. 2018;560(7718):382-386. doi:10.1038/s41586-018-0392-8.
17. Poggio M, *et al*. Suppression of exosomal PD-L1 induces systemic anti-tumor immunity and memory. Cell. 2019;177(2):414-427.e13. doi:10.1016/j.cell.2019.02.016.
18. Lan J, *et al*. M2 macrophage-derived exosomes promote cell migration and invasion in colon cancer. Cancer Res. 2019;79(1):146-158. doi:10.1158/0008-5472.CAN-18-0014.
19. Liu H, *et al*. Colorectal cancer-derived exosomal miR-106b-3p promotes metastasis by down-regulating DLC-1 expression. Clin Sci (Lond). 2020;134(4):419-434. doi:10.1042/CS20191087.
20. Li YY, *et al*. Cancer-associated fibroblasts contribute to oral cancer cells proliferation and metastasis via exosome-mediated paracrine miR-34a-5p. EBioMedicine. 2018;36:209-220. doi:10.1016/j.ebiom.2018.09.006.
21. Zhu G, *et al*. LOXL2-enriched small extracellular vesicles mediate hypoxia-induced premetastatic niche and indicates poor outcome of head and neck cancer. Theranostics. 2021;11(19):9198-9216. doi:10.7150/thno.62455.
22. Palmulli R, Jackson HK, Edgar JR. Tethered exosomes containing the matrix metalloproteinase MT1-MMP contribute to extracellular matrix degradation. J Extracell Vesicles. 2025;14(7):e70122. doi:10.1002/jev2.70122.
23. Jin K, Lan H, Han Y, Qian J. Exosomes in cancer diagnosis based on the latest evidence: where are we? Int Immunopharmacol. 2024;142(Pt A):113133. doi:10.1016/j.intimp.2024.113133.
24. Rayamajhi S, Sipes J, Tetlow AL, Saha S, Bansal A, Godwin AK. Extracellular vesicles as liquid biopsy biomarkers across the cancer journey: from early detection to recurrence. Clin Chem. 2024;70(1):206-219. doi:10.1093/clinchem/hvad176.
25. Van Dorpe S, Tummers P, Denys H, Hendrix A. Towards the clinical implementation of extracellular vesicle-based biomarker assays for cancer. Clin Chem. 2024;70(1):165-178. doi:10.1093/clinchem/hvad189.
26. Araujo-Abad S, *et al*. Exosomes: from basic research to clinical diagnostic and therapeutic applications in cancer. Cell Oncol (Dordr). 2025;48(2):269-293. doi:10.1007/s13402-024-00990-2.
27. Kamerkar S, *et al*. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature. 2017;546(7659):498-503. doi:10.1038/nature22341.
28. Lu Y, *et al*. Tumor microenvironment-derived exosomes: a double-edged sword for advanced T cell-based immunotherapy. ACS Nano. 2024;18(40):27230-27260. doi:10.1021/acsnano.4c09190.
29. Ma C, *et al*. Application of engineered exosomes in tumor therapy. Am J Transl Res. 2025;17(2):736-747. doi:10.62347/KIXF4662.
30. Wang J, Ye J. The role and mechanisms of tumor-derived exosomes in the formation of the premetastatic niche. Cancer Control. 2026;33:10732748261448980. doi:10.1177/10732748261448980.
31. Blavier L, Crnjac A, DeClerck YA. Contribution of tumor-derived extracellular vesicles in the establishment of the pre-metastatic niche: lessons learned from past experimentations and future directions. Clin Exp Metastasis. 2026;43:16. doi:10.1007/s10585-026-10396-z.
32. Wu Y, Han W, Dong H, Liu X, Su X. The rising roles of exosomes in the tumor microenvironment reprogramming and cancer immunotherapy. MedComm. 2024;5(4):e541. doi:10.1002/mco2.541.

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