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REVIEW ARTICLE

The role of melanoma-derived exosomes in metastasis: Challenges and opportunities

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Abstract

Melanoma, a highly aggressive skin cancer, is characterized by its strong metastatic potential and resistance to standard treatments. Recent cancer research has emphasized the significance of exosomes, a type of extracellular vesicle and particle, in mediating cell-to-cell communication and driving tumor progression. Melanoma-derived exosomes contribute to metastasis by facilitating immune evasion, modulating the tumor microenvironment, and inducing epithelial-to-mesenchymal transition. The exosomal cargos, including nucleic acids (DNA, microRNA, long noncoding RNA, and circular RNA), proteins, lipids, and other biomolecules, play critical roles in reprogramming recipient cells to support tumor growth and spread. These exosomes also aid in forming pre-metastatic niches by transferring pro-inflammatory cytokines, extracellular matrix remodeling enzymes, and angiogenic factors to distant organs, preparing these sites for tumor colonization. Furthermore, tumor-derived exosomes promote therapy resistance by delivering drug-resistant molecular signatures, which diminish treatment efficacy. This emerging evidence highlights the therapeutic potential of exosome-based strategies, including inhibitors of exosome biogenesis and uptake or the use of engineered exosomes for targeted drug delivery. Advances in precision medicine also facilitate the use of exosome-derived molecular signatures in early-stage diagnosis and treatment monitoring through liquid biopsy. However, clinical translation remains challenging due to cargo heterogeneity, lack of standardized isolation methods, and potential off-target effects in exosome-based therapies. Addressing these challenges could lead to more effective therapies and better patient outcomes. This review synthesizes current knowledge on the biogenesis, composition, and functional roles of tumor-derived exosomes in metastasis, alongside their potential applications as biomarkers and therapeutic strategies. Deciphering exosomal dynamics in melanoma may open new avenues for advanced diagnostics and treatments.

Keywords: Melanoma; Exosome; Metastasis

1. Introduction

Melanoma is a cancer that originates from pigment-producing cells in the skin.[1] It is known for its aggressive behavior, high propensity for metastasis, and increasing incidence rates worldwide, particularly among young adults.[2] The American Cancer Society reports that melanoma is a leading cause of skin cancer-related deaths, with an estimated 99,780 new cases and 7650 fatalities in the United States in 2022.[3] The disease is classified into several types, including cutaneous melanoma, mucosal melanoma, and uveal melanoma,[4] each presenting unique challenges in terms of diagnosis, treatment, and prognosis.[5-12]

The metastatic process in melanoma is complex and involves several steps: local tissue invasion, entry into the bloodstream or lymphatic system, persistence in circulation, migration into distant tissues, and establishment at secondary sites.[13] Common sites of metastasis include nearby lymph nodes, pulmonary tissue, hepatic tissue, and the brain.[14] The prognosis for patients with metastatic melanoma remains poor, with a 5-year survival rate of <30%.[15] Although significant progress has been made with treatments such as immunotherapy and targeted therapies addressing specific genetic mutations,[16] many patients still experience disease recurrence and progression.[17]

Melanoma cells utilize key molecular pathways, such as the mitogen-activated protein kinase and phosphoinositide 3-kinase-protein kinase B signaling cascades, to drive invasive behavior and survival during metastasis.[18] In addition, immune evasion mechanisms, including the suppression of cytotoxic T-cell responses through programmed death-ligand 1 (PD-L1) expression,[19] further facilitate the metastatic cascade. During this process, melanoma-derived exosomes play a pivotal role in preparing distant organs for tumor colonization by modulating the local microenvironment. These vesicles deliver pro-inflammatory cytokines, extracellular matrix (ECM) remodeling enzymes, and angiogenic factors to distant tissues, fostering a permissive niche for tumor cell invasion.

Recent studies have emphasized the pivotal role of exosomes in cancer development, particularly in metastasis.[20-22] Exosomes, small extracellular vesicles (30 – 150 nm), originate from the endosomal membrane and are secreted into the extracellular space.[23,24] These vesicles transport biomolecules, such as proteins, lipids, and nucleic acids (DNA, long noncoding RNAs [lncRNAs], and microRNAs [miRNAs]), reflecting the molecular traits of their source cells.[25] In melanoma, exosomes actively participate in a wide range of biological processes that contribute to tumor progression and metastasis, including immune modulation, interaction with the tumor microenvironment (TME), and the facilitation of epithelial-to-mesenchymal transition (EMT).[26] The molecular cargos of melanoma-derived exosomes, such as specific DNA, miRNAs, and lncRNAs, have significant potential as indicators for early diagnosis and predictors of treatment outcomes. Furthermore, modified exosomes offer a groundbreaking solution for targeted drug administration, enabling precision medicine approaches that minimize systemic toxicity.

This review aims to provide a comprehensive summary of current knowledge regarding tumor-derived exosomes and their role in metastasis, based on literature from the National Library of Medicine, National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/). We explore the biogenesis and composition of melanoma-derived exosomes, their functional implications in metastasis, and their potential as clinical diagnostics and targeted therapies. By integrating recent findings in exosome research with the broader context of melanoma biology, we aim to highlight the significance of exosomes in shaping the metastatic landscape of melanoma and identify future directions for research and clinical application.

This review covers several key aspects related to melanoma-derived exosomes: (i) the biogenesis and composition of exosomes; (ii) the cargos of exosomes, including nucleic acids, proteins, lipids, and metabolites; (iii) the functional implications of exosomes, particularly their involvement in processes such as proliferation, migration, invasion, immune modulation, and TME remodeling; and (iv) the potential use of exosomes in diagnosis and treatment, including their role as biomarkers, therapeutic targets, and drug delivery systems.

2. Exosome biogenesis and composition

Exosomes are formed through the endosomal pathway, where inward budding of the endosomal membrane generates multivesicular bodies (MVBs).[27,28] Exosomes exhibit significant heterogeneity in size, molecular composition, and biological functions, which complicates their characterization and therapeutic applications. Advanced separation techniques, such as asymmetric-flow field-flow fractionation, have identified distinct extracellular nanoparticle subpopulations, including large exosome vesicles (Exo-L, 90 – 120 nm), small exosome vesicles (Exo-S, 60 – 80 nm), and exomeres (~35 nm, non-membranous nanoparticles).[27] These subtypes carry unique proteomic, lipidomic, and transcriptomic signatures, influencing their roles in tumor progression, immune modulation, and organotropic metastasis. Traditional isolation methods, such as ultracentrifugation and size-

exclusion chromatography, often fail to distinguish these subpopulations, resulting in heterogeneous preparations. Asymmetric-flow field-flow fractionation and immunoaffinity-based separation techniques offer improved resolution, preserving vesicle integrity and specificity. Recognizing exosome heterogeneity and optimizing isolation methods are crucial for advancing biomarker discovery and therapeutic applications.[29] The endosomal sorting complexes required for transport (ESCRT) complex operates in a stepwise manner, with ESCRT-0 identifying ubiquitinated cargo, ESCRT-I and ESCRT-II facilitating membrane curvature, and ESCRT-III completing vesicle separation.[30-32] These MVBs follow two possible pathways: they can merge with lysosomes, leading to their breakdown, or be directed to the plasma membrane, where their contents are discharged into the surrounding extracellular environment as exosomes.[33] The direction of MVB trafficking is influenced by Rab GTPases, such as Rab27a and Rab27b,[34] which facilitate MVB docking and fusion with the plasma membrane, thus promoting exosome release.[35] The biogenesis process is orchestrated by multiple proteins, such as tetraspanins (cluster of differentiation [CD] 63,[36] CD81, and CD9), which are essential for cargo sorting and exosome release. The ESCRT[30] machinery is also integral to the formation of exosomes.[37]

The molecular composition of melanoma-derived exosomes is significantly distinct from that of exosomes secreted by normal cells, as they contain specific proteins, lipids, and nucleic acids that contribute to tumor progression, immune modulation, and metastasis. Tumor-derived exosomes are enriched in proteins associated with tumor progression, such as matrix metalloproteinases (MMPs), integrins, and various oncogenic signaling molecules.[38] In addition, they contain a unique profile of miRNAs that can modulate gene expression in recipient cells, influencing processes such as proliferation, invasion, and immune evasion.[39] Key examples include miR-211,[35] which downregulates the tumor suppressor brain-2 to promote invasion, and miR-155,[40] which suppresses immune cell activation by targeting the suppressor of cytokine signaling 1.

3. Exosomal cargo in melanoma

The cargo of exosomes derived from melanoma cells provides a rich source of information about the tumor's molecular landscape.

3.1. RNA

3.1.1. miRNAs

miRNAs are small RNA molecules that regulate gene expression at the post-transcriptional level. Specific miRNAs are enriched in melanoma-derived exosomes, where they modulate various aspects of tumor biology.[41,42] For instance, miR-211 is associated with the promotion of melanoma cell invasion, while miR-155 is involved in immune modulation.[43] The transfer of these miRNAs to recipient cells can alter their behavior, contributing to the metastatic process.[44,45]

3.1.2. Long non-coding RNAs

Long non-coding RNAs are non-coding RNA molecules longer than 200 nucleotides that influence gene activity through transcriptional, post-transcriptional, and epigenetic mechanisms. In melanoma, certain lncRNAs are selectively packaged into exosomes, where they contribute to tumor progression.[41] For example, lncRNA metastasis-associated lung adenocarcinoma transcript 1 plays a significant role in driving melanoma cell growth and facilitating their migratory behavior.[46] Moreover, studies reveal that metastasis-associated lung adenocarcinoma transcript 1 supports melanoma growth and metastasis by activating critical oncogenic pathways.

3.1.3. Circular RNAs (circRNAs)

circRNAs are a class of non-coding RNAs characterized by their unique covalently bonded circular configuration. They act as competitive endogenous RNAs, sequestering miRNAs and influencing the expression of downstream genes. In melanoma, circRNA cerebellar degeneration-related protein 1 (PD-1) antisense RNA has been identified as a competitive binder of miR-7-5p, which, in turn, stabilizes and upregulates oncogenes like E2F transcription factor 3.[47] This interaction promotes tumor cell proliferation, invasion, and altered glucose metabolism.[48]

3.2. DNA

Exosomal DNA (exoDNA), derived from the cell's nucleus and mitochondria, plays a crucial role in melanoma progression and metastasis. Sorting mechanisms and interactions with endosomal components are involved in its packaging.[50,51]

Studies have shown that tumor-derived exoDNA contains oncogenic mutations, which can be transferred to recipient cells, influencing TME remodeling, immune escape, and drug resistance. In addition, exoDNA serves as a biomarker for liquid biopsy,[52] offering non-invasive diagnostic potential for melanoma.[49,53]

3.3. Proteins

Tumor-derived exosomes carry key regulatory proteins, including MMPs, which degrade the ECM to promote tumor invasion and migration.[30,54] In addition, exosomes transport signaling molecules such as integrins and growth

factors, which facilitate pre-metastatic niche formation and immune modulation.[55,56] Tumor-derived exosomes also contain proteins involved in drug resistance, which modulate therapy responses by altering signaling pathways.[21]

Melanoma-derived exosomes contain a diverse set of proteins that participate in key signaling pathways associated with metastasis. For example, proteins such as MMPs facilitate ECM degradation, allowing for tumor invasion and migration.[57,58] Furthermore, exosomal lipids can modulate signaling networks and influence the activities of recipient cells, further enhancing metastatic potential.[33]

3.4. Lipids

Exosomal lipids play a significant role in melanoma progression by influencing membrane stability, intracellular signaling, and metabolic adaptation.[59] Lipid rafts in exosomes serve as platforms for signal transduction, while specific lipids, such as sphingolipids and ceramides, are involved in cell communication and apoptosis regulation.[60] Dysregulated lipid content in melanoma-derived exosomes has been associated with enhanced metastatic potential and immune evasion.[61]

3.5. Other biomolecules in exosomes

Beyond nucleic acids, proteins, and lipids, melanoma-derived exosomes also contain small metabolites that influence tumor metabolism and interactions with the microenvironment.[39] These metabolites include amino acids, sugars, and vitamins, which support tumor proliferation and modulate immune responses. Glycolytic intermediates found in tumor exosomes contribute to metabolic reprogramming, while vitamins and cofactors regulate oxidative stress and mitochondrial function.[62] Understanding the metabolic landscape of melanoma-derived exosomes could provide novel therapeutic targets for disrupting tumor-supportive pathways.[39]

4. Contribution of melanoma-derived exosomes to metastasis

Exosomes derived from melanoma cells play a multifaceted role in promoting metastasis through various mechanisms:

4.1. Promotion of tumor growth

Exosomes can carry and deliver oncogenic factors, such as growth molecules, including growth regulators and cytokines, to neighboring cells, thereby promoting tumor growth and invasion. For example, melanoma-derived exosomes contain vascular endothelial growth factor, which promotes angiogenesis and enhances tumor vascularization.[63]

4.2. Shaping the TME

Melanoma-derived exosomes are crucial in remodeling the surrounding tumor ecosystem. By transferring bioactive molecules to stromal cells, these exosomes can alter the behavior of the surrounding cells, creating a favorable environment for tumor growth and metastasis.[64] For instance, exosomes can stimulate fibroblasts to produce pro-inflammatory cytokines, leading to increased angiogenesis and enhanced nutrient supply for the tumor. Moreover, exosomes can modify the ECM, making it more conducive to tumor invasion.[65]

4.3. EMT

A key process driven by melanoma-derived exosomes is EMT,[7] a biological mechanism that enables epithelial cells to acquire migratory and invasive characteristics. Exosomal miRNAs, such as miR-211, can downregulate E-cadherin, a key adhesion molecule, promoting EMT and enhancing the invasive capacity of melanoma cells.[6] This transition not only aids in local invasion but also prepares melanoma cells for dissemination to distant organs.[26]

4.4. Immune evasion

Melanoma cells exploit exosomes to evade the immune system. Exosomes can modulate the function of immune cells, including dendritic cells and T-cells, promoting a tolerogenic environment. For instance, melanoma-derived exosomes can carry PD-L1,[66] which binds to programmed cell death PD-1 receptors on T-cells, leading to T-cell inhibition.[67] This immune suppression allows melanoma cells to escape detection and destruction, thereby facilitating their survival and proliferation.[68]

4.5. Pre-metastatic niche formation

Exosomes also contribute to the formation of pre-metastatic niches, which are sites in distant organs that are primed for the arrival and growth of metastatic cells.[64] Melanoma-derived exosomes can induce changes in the microenvironment of these distant sites, such as the lungs or liver, by promoting inflammation and altering the local cellular composition. This pre-conditioning enhances the likelihood of successful colonization by circulating melanoma cells.[69]

4.6. Biomarkers and therapeutic targets

Given their role in metastasis, melanoma-derived exosomes are being explored as potential biomarkers for disease progression and therapeutic targets.[13] The unique molecular signatures of these exosomes can provide insights into tumor dynamics and patient prognosis. Furthermore, targeting exosomal pathways – whether by inhibiting their release, blocking their uptake, or altering

their cargo – could offer a novel therapeutic strategy to combat melanoma metastasis.[70]

5. Diagnostic and therapeutic implications

The unique composition of melanoma-derived exosomes presents opportunities for their use as biomarkers and therapeutic targets.

5.1. Exosomes as biomarkers

Exosomes, which can be extracted from biological fluids such as blood, urine, and lymphatic fluid, show great promise as a resource for liquid biopsies.[71] Specific miRNAs and proteins found in exosomes have been linked to disease progression, treatment outcomes, and prognosis. For example, elevated levels of certain exosomal miRNAs[72] have been identified in advanced stages of melanoma,[73] underscoring their potential as non-invasive biomarkers for early detection and disease monitoring.[74]

5.2. Therapeutic targeting of exosomes

Targeting exosomes represents a promising therapeutic strategy in melanoma, as they contribute to tumor progression, immune modulation, and therapy resistance. Approaches to inhibit exosome release, modify their cargo, or block their uptake could disrupt tumor-promoting communication pathways. In addition, engineered exosomes offer potential for targeted drug delivery, improving therapeutic efficacy while minimizing off-target effects.[22]

However, off-target effects remain a major concern, as these therapies may affect non-target tissues, leading to unwanted side effects and reduced efficacy. Exosomes can interact with unintended cell types, potentially causing non-specific distribution and unintended interactions. The biodistribution of exogenously administered exosomes is often unpredictable, resulting in unintended accumulation in non-target organs or tissues. This non-specific distribution can lead to unwanted side effects, such as inflammation or toxicity in healthy tissues, thereby compromising overall therapeutic efficacy. These limitations are further discussed in Section 4.3, which provides a more comprehensive perspective on the challenges associated with the clinical application of exosome-based therapies.

Recent studies have identified several key exosomal proteins, signaling pathways, and RNA molecules as potential therapeutic targets in melanoma. Regulators of exosome biogenesis, cargo sorting, and uptake play crucial roles in metastasis and immune evasion. For example, Rab GTPases,[75] tetraspanins, and ESCRT-associated proteins influence exosome secretion and composition, affecting interactions with the TME.[76,77] Similarly, targeting oncogenic exosomal RNAs, such as miRNAs and long non-coding RNAs, offers a novel approach to suppress tumor growth and immune escape.[78,79]

The table below summarizes exosome-associated therapeutic targets in melanoma[80,81] (Table 1).

By targeting exosome-associated molecules and pathways, novel therapeutic strategies could limit melanoma progression, enhance immune responses, and improve drug delivery efficiency, thereby offering new directions for precision oncology.

5.3. Limitations and challenges of exosome-based therapies in melanoma

Exosome-based therapeutic strategies show great potential in the treatment of melanoma by targeting metastatic pathways and modulating the immune system. However, the clinical application of exosome-based therapies faces significant challenges. One significant obstacle is the heterogeneity of exosomal cargo, which complicates the predictability and effectiveness of treatments. Exosomes are naturally heterogeneous, carrying a wide variety of proteins, lipids, and RNAs, depending on their cell of origin and the conditions under which they are produced. This variability makes it difficult to standardize exosome preparations, which can result in inconsistent therapeutic outcomes. Differences in cargo composition can lead to unpredictable interactions with target cells, further complicating clinical applications.

Off-target effects remain a major concern for exosome-based therapies. These therapies may affect non-target tissues, leading to undesirable side effects and reduced therapeutic efficacy. Exosomes can interact with unintended cell types, potentially leading to non-specific distribution and unintended interactions. The biodistribution of exogenously administered exosomes is often unpredictable, resulting in unintended accumulation in non-target organs or tissues. This non-specific distribution can lead to side effects such as inflammation or toxicity in healthy tissues, thereby compromising the overall therapeutic efficacy. In addition, exosomes may bind to non-target receptors or cells, further increasing the risk of adverse reactions. These off-target interactions not only reduce treatment effectiveness but also pose significant safety concerns, limiting the widespread use of exosome-based therapies.

A significant challenge in the clinical translation of exosome-based therapies is the scalability of exosome production. Producing exosomes in large quantities with consistent quality and potency remains a major hurdle. The isolation and purification methods for exosomes need

Table 1. Melanoma-derived exosomes as therapeutic targets

Target	Function and role in exosomes	Therapeutic potential	References
CEMIP	Enhances exosome-mediated tumor invasion and metastasis	Inhibiting CEMIP reduces metastasis potential	22
Rab27a/b	Regulates exosome secretion and cargo release	Rab inhibitors can block tumor exosome release	75
Syntenin-1	Facilitates sorting of tumor-promoting proteins into exosomes	Suppressing syntenin-1 reduces exosomal pro-metastatic factors	76
HSP90	Involved in the exosomal transport of oncogenic signaling proteins	HSP90 inhibitors block exosomal stress responses	77
Tetraspanins (CD9, CD63, CD81)	Regulate exosome biogenesis and uptake in recipient cells	Potential for exosome-based drug delivery modifications	78
Alix	Controls ESCRT-mediated exosome formation	Alix inhibitors could disrupt melanoma exosome secretion	79
Integrins (ITGαvβ3, ITGα6β4)	Direct exosomes to specific metastatic sites	Targeting integrins can block organotropic metastasis	82
PD-L1	Delivered by tumor exosomes to suppress immune response	Anti-PD-L1 therapy enhances anti-tumor immunity	67
MicroRNAs (miR-155, miR-211)	Modulate tumor progression and immune evasion via exosomes	Blocking oncogenic miRNAs may reduce melanoma progression	83
HSP70	Promotes exosome-mediated stress adaptation	HSP70 inhibitors may impair tumor exosome function	81

Abbreviations: CD: Cluster of differentiation; CEMIP: Cell migration-inducing and hyaluronan-binding protein; ESCRT: Endosomal sorting complexes required for transport; HSP: Heat-shock protein; PD-L1: Programmed death-ligand 1.

to be optimized for clinical use to ensure both purity and consistency. Moreover, immunogenicity poses another challenge, as exosomes derived from non-autologous sources may trigger immune responses in the recipient, reducing their therapeutic efficacy. The long-term safety profile of exosome-based therapies is still not fully understood, requiring extensive research and clinical trials to assess potential risks. Furthermore, the lack of standardized protocols for exosome preparation, isolation, and characterization complicates the consistency of clinical outcomes. Clear regulatory guidelines are needed to ensure the safety and efficacy of exosome-based therapies in clinical settings.

Efficient targeted delivery of exosomes remains a critical challenge in maximizing therapeutic benefits. While exosomes hold promise for targeted delivery of therapeutic agents, their ability to reliably reach specific tissues or cells is often inconsistent. Developing strategies to enhance the specificity of exosome targeting is crucial for improving treatment outcomes and minimizing off-target effects. Advances in surface modification techniques, such as functionalizing exosomes with targeting ligands, are required to improve their specificity and efficacy. Targeting specific cell types or tissues with exosomes will be key to overcoming current limitations and ensuring that exosome-based therapies achieve their full therapeutic potential.

5.4. Emerging exosome-based therapeutic strategies

Recent advances have highlighted the therapeutic potential of engineered exosomes as both therapeutic agents and delivery systems for various diseases, including melanoma. Through genetic modification, surface engineering, and cargo loading, exosomes can be tailored to enhance targeting ability, improve drug delivery efficiency, and reduce systemic toxicity.[84] By modifying exosomal membranes or incorporating bioactive molecules, researchers aim to refine their specificity and therapeutic efficacy while minimizing off-target effects.[85]

One promising approach involves modifying exosome cargo to enhance cancer immunotherapy. Tumor-derived exosomes carrying tumor-associated antigens can stimulate antigen-presenting cells, thereby strengthening the anti-tumor immune response. In addition, engineered exosomes depleted of PD-L1, a key immune checkpoint regulator, have been explored to enhance the effectiveness of PD-1/PD-L1 inhibitors in melanoma therapy.[86] These findings indicate that engineered exosomes may complement current immunotherapies.

In the context of chemotherapy, exosomes have been modified to serve as drug carriers, improving the delivery of cytotoxic agents such as paclitaxel, doxorubicin, and cisplatin.[87] Compared to synthetic nanoparticles, exosomes

demonstrate superior biocompatibility, increased stability, and enhanced uptake by tumor cells, making them promising vehicles for precision medicine.[88] Moreover, exosome-mediated clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) gene editing has been explored as a tool to selectively disrupt oncogenic mutations, offering a novel therapeutic avenue in melanoma.[89]

Beyond oncology, engineered exosomes have shown significant promise in regenerative medicine, particularly in wound healing, neuroregeneration, and cardiac repair. Studies have demonstrated that mesenchymal stem cell-derived exosomes, enriched with growth factors such as vascular endothelial growth factor, transforming growth factor beta, and insulin-like growth factor 1, accelerate wound closure, angiogenesis, and tissue remodeling, making them attractive candidates for skin regeneration and chronic wound therapy.[90] In neurological disorders, exosomes carrying neurotrophic factors such as brain-derived neurotrophic factor and nerve growth factor have been tested for their potential to promote neuronal survival, axonal growth, and synaptic plasticity, showing therapeutic promise in conditions like Alzheimer's disease, Parkinson's disease, and spinal cord injury.[91]

Another growing application of engineered exosomes is in cardiovascular repair, where exosomes loaded with pro-angiogenic miRNAs (miR-21, miR-126, and miR-199a) have been shown to promote blood vessel formation, reduce ischemic injury, and enhance heart function following myocardial infarction.[92] These studies suggest that exosome-mediated therapy could offer a novel approach to treating ischemic heart disease and other cardiovascular disorders.

The ability to fine-tune exosomal cargos and surface properties has also enabled their use in autoimmune and inflammatory diseases. By engineering exosomes to carry anti-inflammatory cytokines (e.g., interleukin-10 and transforming growth factor-beta) or immunosuppressive RNAs, researchers have explored their application in conditions such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease.[93] These modified exosomes have shown potential in reducing inflammation, modulating immune responses, and promoting tissue repair, further expanding their therapeutic scope.

Despite these advancements, several challenges remain in exosome-based therapeutics, including scalability, reproducibility, and regulatory hurdles. The development of standardized isolation and purification techniques is crucial for ensuring the consistency and safety of exosome-based interventions. In addition, efforts to enhance exosome targeting specificity and prolong circulation time are actively being pursued to improve their therapeutic effectiveness in clinical settings.

The table below summarizes key applications of engineered exosomes in various therapeutic fields (Table 2).

5.5. Integration of exosomes with precision medicine

The unique biomarker properties of exosomes have the potential to significantly advance precision medicine,[94] particularly in the diagnosis and personalized treatment of melanoma. For example, liquid biopsy techniques that analyze exosomal miRNA expression profiles can identify patients at high risk of metastasis, providing critical insights for the early intervention. Furthermore, in the therapeutic realm, engineered exosomes can serve

Table 2. Therapeutic applications of engineered exosomes

Application	Modification strategy	Therapeutic potential	References
Cancer immunotherapy	Exosomes carrying tumor-associated antigens	Enhances antigen presentation and T-cell activation	85
Immune checkpoint blockade	PD-L1-depleted exosomes	Improves anti-PD-1 therapy efficacy	86
Chemotherapy	Drug-loaded exosomes (paclitaxel, doxorubicin, and cisplatin)	Targeted drug delivery with reduced systemic toxicity	88
Gene therapy	CRISPR/Cas9-loaded exosomes	Oncogene editing for precision cancer treatment	89
Wound healing	MSC-derived exosomes with growth factors	Accelerates tissue repair and reduces scarring	90
Neuroregeneration	Exosomes carrying BDNF, NGF, and miR-124	Supports neuronal survival and axonal repair	91
Cardiac repair	Exosomes with pro-angiogenic microRNAs (miR-21, miR-126)	Stimulates blood vessel formation and improves heart function	92
Autoimmune diseases	Immunomodulatory exosomes enriched in IL-10 and TGF-β	Reduces inflammation and modulates immune responses	93

Abbreviations: BDNF: Brain-derived neurotrophic factor; Cas9: CRISPR-associated protein 9; CRISPR: Clustered regularly interspaced short palindromic repeats; IL-10: Interleukin-10; miR: MicroRNA; MSC: Mesenchymal stem cell; NGF: Nerve growth factor; PD-L1: Programmed death-ligand 1; PD-1: Programmed cell death protein 1; TGF-β: transforming growth factor-beta.

as precise drug delivery systems, transporting anti-cancer drugs, small interfering RNAs, or CRISPR/Cas9 gene-editing tools[95] directly to tumor cells while minimizing damage to normal tissues. For instance, encapsulating chemotherapeutic agents within exosomes and delivering them to melanoma sites not only enhances therapeutic efficacy but also substantially reduces systemic toxicity. By integrating exosomal biomarker analysis with targeted delivery technologies, precision medicine holds the promise of optimizing the full spectrum of melanoma management, thereby significantly improving patient survival rates and quality of life (Figure 1).

6. Discussion

The intricate relationship between tumor-derived exosomes and metastasis underscores a significant advancement in our understanding of tumor biology and the mechanisms underlying cancer progression. Exosomes are small extracellular vesicles secreted by various cell types, including melanoma cells. They facilitate cell communication and transport a diverse array of molecular cargo, including proteins, lipids, and nucleic acids. In the context of melanoma, these vesicles play a multifaceted role in promoting metastasis by influencing the TME,[98] enhancing the invasive properties

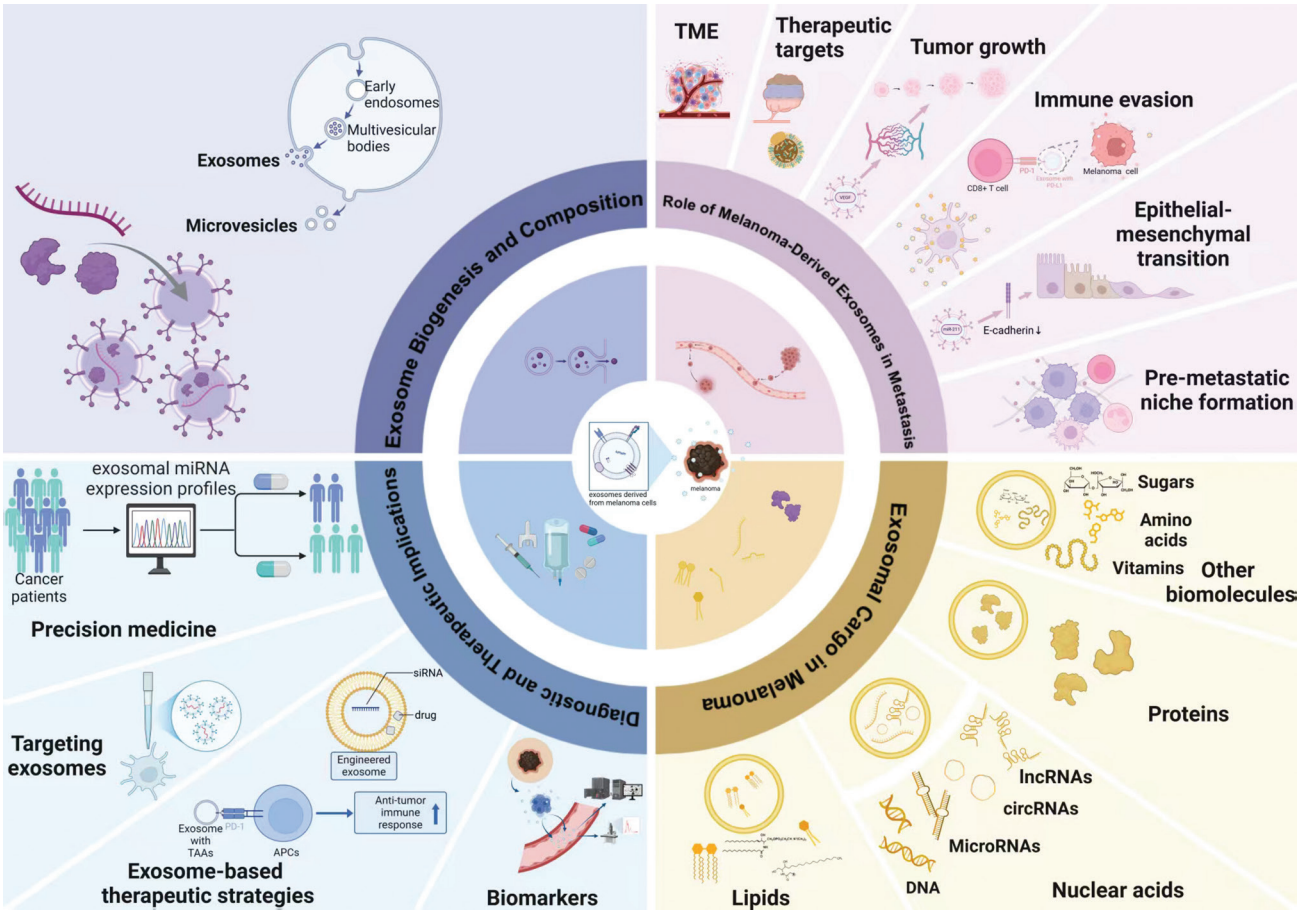


Figure 1. The multifaceted role of melanoma-derived exosomes in metastasis and therapeutic potential. This figure provides a comprehensive overview of the biogenesis, molecular composition, and functional implications of melanoma-derived exosomes. The upper-left section illustrates the process of exosome biogenesis, from their formation within MVBs to their release into the extracellular space. The lower-right section categorizes the diverse molecular cargos in exosomes into nucleic acids (miRNAs, circRNAs, lncRNAs, messenger RNAs, and DNA fragments), proteins (MMPs, integrins, heat shock proteins, and oncogenic factors), lipids (sphingolipids, cholesterol, and phospholipids), and other biomolecules (metabolites, glycoproteins, and growth factors). These components reflect the exosomes' cellular origin and mediate their pro-metastatic effects. The upper-right region highlights their critical roles in tumor metastasis, including TME[96] remodeling, immune evasion, EMT,[97] and pre-metastatic niche formation, which collectively facilitate both local and distant progression. Finally, the lower-left panel explores the diagnostic and therapeutic potential of tumor-derived exosomes, including their role as biomarkers for liquid biopsy, as well as their potential as therapeutic targets and delivery vehicles. Exosome-based strategies are being investigated for targeted drug delivery, RNA-based therapy, and immunomodulation in melanoma treatment. This integrated representation underscores the central role of exosomes in melanoma metastasis and offers a conceptual framework for future research. Image created by authors.
Abbreviations: APC: Antigen-presenting cell; CD8: Cluster of differentiation 8; miR: MicroRNA; PD-L1: Programmed death-ligand 1; PD-1: Programmed cell death protein 1; TAAs: Tumor-derived exosomes carrying tumor-associated antigens; VEGF: Vascular endothelial growth factor.

of tumor cells, and facilitating immune evasion.[39] The cargos within melanoma-derived exosomes are enriched with specific miRNAs, such as miR-211 and miR-155, which influence key pathways involved in tumor progression. For example, miR-211 can downregulate E-cadherin, a crucial adhesion molecule, promoting EMT, which, in turn, enhances tumor cell migration and invasion.[99,100] This transition is not merely isolated but is intricately linked to the TME, where exosomes can reshape surrounding stromal and immune cells, fostering a tumor-supportive niche.[101]

Moreover, tumor-derived exosomes contribute to immune cell reprogramming[102] by downregulating the expression of major histocompatibility complex molecules and promoting the development of regulatory T-cells.[103] This immune modulation is crucial for melanoma cells to escape immune surveillance, allowing for unchecked growth and metastasis.[68] The exosome-mediated transfer of bioactive molecules to distant sites further complicates the metastatic process, as exosomes establish pre-metastatic niches by modifying distant organ phenotypes, thereby enhancing melanoma cell colonization. For example, exosomal factors can induce a pro-inflammatory environment in the lungs or liver, promoting the survival and colonization of metastatic melanoma cells.[69]

Exosomes are not only promising therapeutic tools but also valuable diagnostics biomarkers. Their cargo of tumor-specific proteins and nucleic acids makes them ideal candidates for early melanoma detection and for monitoring treatment responses. Combining exosome-targeting strategies with current therapies, such as immune checkpoint inhibitors or targeted drugs, could further enhance therapeutic effectiveness by modulating the TME.

As potential biomarkers,[104] tumor-derived exosomes offer a non-invasive method for tracking disease progression and treatment response. Their unique molecular signatures provide insights into the genetic and epigenetic features of tumors, aiding in the development of personalized treatment strategies.[105] However, the clinical application of exosomes as biomarkers is hindered by challenges in standardizing isolation and characterization methods,[106] as well as validating their utility across diverse patient populations. The heterogeneity of exosomal populations and the dynamic nature of their cargo further complicate these efforts, necessitating robust methodologies to ensure reproducibility and reliability in clinical settings.[65]

Therapeutically, targeting exosomal pathways presents an innovative strategy to disrupt the communication that underpins melanoma metastasis.[107,108] Approaches such as inhibiting exosome biogenesis or blocking their uptake by recipient cells could limit the pro-metastatic effects of these vesicles. In addition, engineered exosomes are emerging as promising vehicles for targeted drug delivery, allowing for the specific delivery of therapeutic agents directly to tumor cells or the TME.[109] This strategy not only enhances the efficacy of treatments but also minimizes off-target effects, which is a significant advantage in the context of systemic therapies for melanoma.[110] Beyond inhibiting exosome biogenesis or blocking their uptake, the development of engineered exosomes offers transformative potential. Recent advancements in nanotechnology have enabled the design of exosomes with enhanced specificity, such as through surface modification with ligands or CRISPR/Cas9-mediated editing of their cargo,[111] optimizing the delivery of therapeutic agents to tumor cells or the TME. Furthermore, exosomes are increasingly recognized for their role as non-invasive biomarkers, facilitating early detection of melanoma and monitoring treatment response through liquid biopsies. Combining exosome-based therapies with immune checkpoint inhibitors or traditional treatments, such as targeted therapies and radiotherapy, could amplify therapeutic efficacy and overcome resistance mechanisms. However, challenges remain, including the need for more refined isolation techniques, mitigation of off-target effects, and a comprehensive understanding of their long-term safety profile. Addressing these hurdles through innovative research will unlock the full potential of exosomal therapies, establishing them as a cornerstone in melanoma treatment strategies. Despite significant advancements in melanoma treatment with immunotherapies and targeted therapies, several limitations remain, including off-target effects, the development of resistance to treatment, and limited effectiveness against metastatic melanoma. These challenges highlight the need for more effective and alternative treatment strategies, such as exosome-based therapies. The long-term efficacy of current therapies is often hindered by these issues, necessitating the development of strategies that can overcome these obstacles.

However, the complexity of exosomal biology demands further investigation into their biogenesis, cargo selection, and interactions within the TME. Understanding the signaling pathways that regulate exosome release and uptake will be crucial for deciphering their role in metastasis. Furthermore, research should focus on the interplay between exosomes and other components of the TME, including ECM elements and various immune cell populations, to better understand how these interactions facilitate melanoma progression.[112]

New technologies, such as next-generation sequencing and advanced imaging techniques, offer promising avenues for exploring exosomal dynamics *in vivo*.[113] Future research should validate exosomal cargo functions, their

impact on recipient cells, and the development of exosome-based therapies. By integrating exosomal research with existing melanoma treatment paradigms, we can enhance our understanding of the disease and improve patient outcomes.

The major challenges in exosome-based therapeutics stem from their heterogeneity, lack of standardized isolation and characterization methods, and regulatory barriers.[114] The diversity of exosomes, including variations in their protein, lipid, and nucleic acid cargos, poses challenges for clinical applications. This variability complicates the prediction of biological behavior and consistency in therapeutic outcomes.[37,115] Future research should focus on isolating functionally distinct exosome subpopulations to improve specificity and efficacy. The absence of standardized isolation and characterization methods limits the reproducibility and scalability of exosome-based therapies.[116] Developing robust, cost-effective, and scalable isolation techniques, alongside standardized protocols, is essential for clinical applications and inter-study comparability.[117] The clinical translation of exosome therapies also faces regulatory challenges, including concerns about safety, efficacy, and quality control. Collaboration among researchers, clinicians, and regulators is crucial for establishing clear guidelines and accelerating the approval processes.[118] Overcoming these barriers will enhance the potential of exosome-based therapies, advancing melanoma treatment and patient care.[119]

In conclusion, research on tumor-derived exosomes and their role in metastasis opens new avenues for both diagnostic and therapeutic strategies. Advancing knowledge of exosomal biology may transform melanoma management by identifying new therapeutic targets and enhancing patient outcomes.[120] The integration of exosomal research into clinical practice will require collaborative efforts across disciplines, encompassing molecular biology, immunology, and clinical oncology, to fully harness the potential of these vesicles in combating melanoma metastasis.

7. Conclusion

Melanoma-derived exosomes play a critical role in the metastatic process by influencing tumor growth, immune evasion, and the remodeling of the TME. Their unique molecular composition provides valuable insights into the biology of melanoma and offers potential avenues for diagnosis and treatment. Exosomes have shown promise as therapeutic tools due to their natural biocompatibility, ability to cross biological barriers, and potential for engineering to deliver therapeutic molecules such as RNA, proteins, or drugs. Recent studies have highlighted their utility in targeted drug delivery and enhancing immunotherapies like anti-PD-1 treatments.

However, significant challenges remain in translating these findings into clinical applications. The inherent heterogeneity of exosome cargo introduces variability in therapeutic efficacy, complicating their use as consistent treatment tools. Furthermore, the lack of standardized isolation methods and characterization protocols limits reproducibility and scalability for clinical use. Regulatory barriers, including concerns about safety, immunogenicity, and quality control, further hinder the transition from research to clinical practice.

Future research should prioritize overcoming these challenges by developing advanced technologies for isolating and characterizing exosomes, identifying functionally distinct subpopulations, and addressing regulatory requirements. By tackling these barriers, exosome-based approaches hold great potential to unlock new opportunities for effective melanoma therapies and broader applications in oncology.

Despite the promising potential of exosome-based therapies, their clinical translation faces significant barriers, including the variability of exosome cargo, the difficulty of achieving consistent isolation and purification, and regulatory challenges in developing exosome-based therapeutics. In addition, improving the targeting specificity of exosomes to reduce off-target effects and enhance their therapeutic efficacy will be crucial for the successful application of exosome-based therapies in clinical settings.

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Conflict of interest

The authors declare that they have no competing interests.

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