D J Med Sci 2025;11(3):159-168
doi: 10.5606/fng.btd.2025.199

Review

Exosomes in cancer progression: Orchestrators of EMT, pre-metastatic niches, and therapy resistance

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ABSTRACT

Exosome-mediated communication has become a crucial mechanism by which tumor and stromal cells synchronize malignant behavior. These nanoscale vesicles function as dynamic carriers, delivering a varied array of functional molecules that facilitate critical tumor-promoting processes, such as fibroblast activation, extracellular matrix remodeling, metabolic reprogramming, and immune modulation. Cancer cells dynamically adjust to environmental stress, circumvent therapeutic pressure, and create pre-metastatic niches through these multifactorial actions. Increasing evidence indicates that exosome-derived RNAs and proteins contribute to drug resistance and hold promise as predictive biomarkers of treatment response. This review summarizes recent advances in understanding how exosome-driven molecular interactions integrate signaling and metabolic networks to promote tumor progression. Furthermore, it highlights the translational potential of targeting exosomal pathways as a novel therapeutic strategy to overcome resistance and improve cancer treatment.

Keywords: Cancer, cancer micro-environment, drug-resistance, exosome.

Intercellular communication within the tumor microenvironment (TME) is a crucial factor influencing cancer progression, metastasis, and therapeutic efficacy. Exosome-mediated signaling has garnered significant attention among cellular interaction modes for its ability to transfer various bioactive molecules between tumor and stromal cells. These nanoscale vesicles transport proteins, RNAs, lipids, and metabolites that collectively govern extracellular matrix (ECM) remodeling, fibroblast activation, and immune modulation. Through these actions, exosomes alter metabolic pathways and facilitate the emergence of drug resistance.[1]

Exosomes establish a communicative network through dynamic molecular exchange, thereby augmenting tumor plasticity and resilience in stressful conditions. Comprehending the molecular mechanisms governing this vesicular communication is crucial for clarifying processes such as epithelial-mesenchymal transition (EMT), metabolic reprogramming, and immune evasion. This review summarizes current insights into exosome-mediated tumor progression and therapy resistance, highlighting their potential roles as diagnostic biomarkers and therapeutic targets in cancer management.

TUMOR PROGRESSION: EXOSOME-MEDIATED MECHANISM

Tumor cell-fibroblast signaling

Tumor-derived exosomes (TDEs) play a decisive role in shaping the malignant TME by activating stromal fibroblasts and driving their conversion into cancer-associated fibroblasts (CAFs). Key exosomal proteins, including transforming growth factor beta (TGF-β) and wingless-related integration site (Wnt) ligands, have been demonstrated to induce this transformation. For instance, bladder cancer-derived exosomes

Received: November 17, 2025
Accepted: December 11, 2025
Published online: January 28, 2026

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Cite this article as:
Camci IY, Aysan A, Ersezen N, Caglayan I. Exosomes in cancer progression: orchestrators of EMT, pre-metastatic niches, and therapy resistance. D J Med Sci 2025;11(3):159-168. doi: 10.5606/fng.btd.2025.199.

transfer TGF-β, inducing SMAD signaling and CAF marker expression, whereas cervical carcinoma-derived exosomes enriched in Wnt2B activate canonical Wnt/β-catenin signaling, promoting fibroblast proliferation and myofibroblastic differentiation.[2,3] In addition, it has been demonstrated that tumor exosomal microRNAs (miRNAs), including miR-21 and miR-9 in breast cancer, have the capacity to reprogram fibroblast gene expression, thereby reinforcing CAF-like phenotypes.

Once activated, CAFs release an array of matrix-remodeling enzymes [e.g., matrix metalloproteinases (MMPs), lysyl oxidase] and cytokines [e.g., TGF-β, interleukin-6 (IL-6), CXC motif chemokine ligand 12] that enhance tumor proliferation, invasion, angiogenesis, and immune evasion, sustaining a reciprocal tumor–stroma feedback loop.[4] This bidirectional communication is further amplified by CAF-derived exosomes, which shuttle oncogenic factors, such as Wnt10B, back to tumor cells, activating β-catenin signaling and inducing EMT-related transcriptional programs. Notably, loss of the tumor suppressor p85α in CAFs augments Wnt10B exosomal release and accelerates cancer cell invasion.[5]

Collectively, these findings describe a dynamic exosome-mediated signaling axis in which tumor cells and fibroblasts reciprocally reprogram each other, establishing a microenvironment that favours malignancy and EMT-driven progression.

Angiogenesis and the interaction of endothelial cells

Exosomes are also involved in cancer progression by stimulating angiogenesis. They can transport pro-angiogenic molecules such as vascular endothelial growth factor (VEGF), MMPs, and miRNAs, and by such mechanisms, TDEs transfer these angiogenic molecules to endothelial cells and support angiogenesis.[6]

Recent studies have shown that exosomal cargo modulates endothelial cell behavior through multiple mechanisms. Tumor-derived exosomes carrying miR-210 enhance endothelial cell migration and tube formation by targeting Ephrin-A3 (EFNA3) and activating VEGF signaling pathways.[7] Similarly, miR-23a transferred via hypoxic lung cancer exosomes promotes angiogenesis by inhibition of prolyl hydroxylase and stabilization of hypoxia-inducible factor 1α (HIF-1α), leading to increased VEGF activity in endothelial cells.[8]

Recent studies demonstrate that exosomes directly affect endothelial cell function, substantially regulating angiogenesis. It has been reported that exosomes derived from tumors stimulate endothelial cell proliferation, migration, and tube formation. Exosomes secreted by colorectal cancer cells target the GNAI1 gene via the miR-320d they contain, activating the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) signaling pathway, which subsequently elevates VEGFA expression, thereby augmenting both angiogenesis and metastatic capability.[9] Conversely, exosomes originating from endothelial progenitor cells (EPCs) have been reported to exhibit protective effects in regenerative and vascular repair mechanisms. The EPC-derived exosomes enhance proliferation, diminish apoptosis, and augment angiogenic capacity in lipopolysaccharide (LPS)-injured brain microvascular endothelial cells via the miR-126a-5p pathway they transport.[10]

Likewise, exosomes derived from EPCs have been documented to ameliorate vascular endothelial injury and re-establish vessel integrity through the modulation of the Bcl2/Bax/Caspase-3 pathway.[11] Moreover, it has been noted that exosomes released during inflammatory or tissue damage conditions can modulate endothelial functions. Exosomes obtained from human deciduous tooth- derived stem cells and induced by apoptosis enhanced tube formation and branching in Human Umbilical Vein Endothelial Cells (HUVEC) cells; this phenomenon was correlated with pro-angiogenic proteins including Aminopeptidase N/Cluster of Differentiation 13 (APN/CD13) and MMP-2.[12] In addition to RNA molecules, exosomal proteins such as MMP-2, MMP-9, and integrins (αvβ3, α6β4) contribute to angiogenesis by degrading the ECM and facilitating endothelial cell migration, thereby promoting angiogenic activity.[13] Integrins on exosomes are particularly important in directing organ-specific metastasis by priming vascular niches in distant organs.[14] Moreover,

tumor exosomes influence the vascular microenvironment indirectly by interacting with pericytes, fibroblasts, and tumor-associated macrophages, further enhancing angiogenesis.[15]

Exosome-mediated angiogenesis also plays a role in resistance to anti-angiogenic therapies. For example, bevacizumab-resistant glioblastoma cells release exosomes enriched with VEGF-A and miR-21, which sustain angiogenic signaling even under VEGF receptor blockade.[16] From a translational perspective, circulating exosomal miRNAs, proteins, or long non-coding RNAs (lncRNAs) may serve as biomarkers of angiogenic activity and tumor progression, informing prognosis or predicting response to anti-angiogenic therapies.[17]

Experimental work demonstrated that extracellular vesicles (EVs) isolated directly from mouse tumor tissue induced endothelial migration, vessel formation, and angiogenesis *in vivo* through macrophage-derived VEGF production, proving that tumor-derived EVs act as functional angiogenic mediators in physiological tumor environments.[18] In addition, M2 macrophage-derived exosomes significantly enhanced HUVEC proliferation, migration and tube formation, revealing that stromal cell-derived exosomes actively participate in tumor neovascularization.[19] Furthermore, tumor-derived exosomal miR-3157-3p was shown to directly induce vascular permeability and angiogenesis by suppressing Tissue Inhibitor of Metalloproteinases/Krüppel-Like Factor 2 (TIMP/KLF2) signaling, resulting in enhanced metastatic capacity *in vivo* Non-Small Cell Lung Cancer (NSCLC) tumor xenograft model.[20] Taken together, the findings presented in this section underline the multifaceted role of TDEs in regulating endothelial dynamics, extracellular remodeling, and angiogenic responsiveness within the TME.

Immune modulation

Exosomes can be secreted by both healthy and tumor cells, and they are important molecules for shaping the TME by various mechanisms.[13,21] They exert their effects by transferring cargoes to both tumor cells and healthy cells, including fibroblasts, endothelial cells, and leukocytes in the TME. Depending on the type of cancer and the biomolecular content of exosomes taken up by target cells, various effects may occur, such as promoting tumor growth, metastasis, angiogenesis, inflammation, and immune remodeling. By transferring molecules which are important for cellular pathways such as Phosphoinositide 3-kinase/Protein kinase B (PI3K/AKT), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and mechanistic target of rapamycin (mTOR), exosomes can promote cancer cell proliferation, invasion, and migration. Furthermore, drug resistance of exosome-recipient cells can also be influenced by the content of exosomes. For example, exosomes carrying low amounts of miR-100-5p secreted by cisplatin-resistant lung cancer cells can induce chemoresistance in recipient lung cancer cells.[21]

Exosomes secreted by tumor cells or healthy cells in the TME can support immunosuppression. To escape from the immune system, tumor cells can release exosomes containing immune checkpoint proteins such as programmed death-ligand 1 (PD-L1); by reaching the circulation, these tumor-derived exosomes can suppress the anti-tumor activity of T cells.[22] Exosomes can exert different immunosuppressive effects on the immune system, ultimately promoting tumor growth, invasion, metastasis, and resistance to immunotherapies. In addition to T cells, exosomes can affect other immune cells, including dendritic cells, macrophages, and natural killer (NK) cells. Recent studies have revealed specific molecular mechanisms by which exosomes modulate immune cells. Tumor-derived exosomes carrying miR-21 and miR-222 polarise macrophages toward an M2 immunosuppressive phenotype by activating STAT3 signaling.[7] Glioma exosomes enriched with miR-1246 can suppress macrophage antitumor activity through nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) pathway modulation.[8]

Exosomes also impair dendritic cell maturation and antigen presentation; for example, lung cancer exosomes carrying galectin-9 reduce the expression of major histocompatibility complex (MHC) class II in dendritic cells, decreasing T cell priming.[23] The NK cell cytotoxicity can be suppressed by tumor exosomal TGF-β and

miR-23a, which downregulate NKG2D receptor expression.[13] Circulating exosomal PD-L1 is associated with poor response to programmed death-1 (PD-1)/PD-L1 blockade therapies.[14] Strategies that inhibit exosome biogenesis, prevent exosome uptake, or neutralise exosomal PD-L1 are being investigated to overcome immune evasion and enhance therapeutic outcomes.[15]

Recent studies demonstrated that tumor-derived EVs expressing PD-L1 directly inhibited $CD8^+$ T-cell activity and acted as decoys for anti-PD-L1 antibodies, resulting in reduced immunotherapy efficacy.[24] Moreover, gastric cancer-derived exosomal PD-L1 was shown to promote the expansion of myeloid-derived suppressor cells, thereby reinforcing immune evasion and tumor progression.[25] Additionally, prostate cancer-derived exosomes were shown to upregulate PD-L1 expression in macrophages via the PI3K/AKT pathway, establishing a direct mechanistic link between exosomal signaling and immune suppression.[26] Altogether, the findings discussed above illustrate how exosomes function as central mediators of communication between tumor cells and the immune system, profoundly influencing immune surveillance, immune escape, and tumor progression.

EXOSOME-MEDIATED EMT AND PRE-METASTATIC NICHE FORMATION

Exosomes are key mediators of intercellular communication that coordinate EMT, stromal remodeling, and pre-metastatic niche (PMN) formation. These nanosized EVs, containing proteins, lipids, and nucleic acids, profoundly influence the TME.[27]

Tumor-derived exosomes remodel the ECM, alter endothelial integrity, and initiate stromal activation at pre-metastatic sites.[28] Multiple studies demonstrate that exosomes activate canonical EMT pathways-including TGF-β/SMAD, Wnt/β-catenin, PI3K/AKT, and NF-κB-resulting in the induction of EMT-related transcription factors and enhanced invasive behavior.[17,29-31]

Exosomal cargoes such as MMPs, Wnt ligands, and miRNAs accelerate ECM degradation and initiate EMT-associated transcriptional programs. For example, melanoma exosomal miR-21 increases MMP-2 and MMP-9 in fibroblasts, whereas triple-negative breast cancer exosomes enriched in MMP-1 activate protease-activated receptor-1 (PAR1)-dependent EMT.[32,33]

Wnt-containing exosomes (Wnt1, Wnt4, Wnt5a, Wnt10b) promote β-catenin activation and induce mesenchymal transformation in target epithelial cells.[25] Stromal cells-particularly CAFs-further amplify EMT induction. The CAF-derived vesicles carrying MMP2, MMP9, and TGF-β promote ECM stiffening and collagen crosslinking, enhancing EMT via Yes-Associated Protein/Transcriptional Co-Activator with PDZ-binding motif (YAP/TAZ) and Wnt/β-catenin signaling.[28,34]

Exosomes from CAFs enriched in miR-34a-5p or circular RNAs (circRNAs) further promote β-catenin/SNAIL-dependent EMT in colorectal and oral cancers.[35,36] Furthermore, exosomal miR-21 facilitates bidirectional communication between tumor cells and fibroblasts, sustaining ECM remodeling and invasion.[31]

Exosomes additionally contribute to PMN formation by regulating endothelial permeability and stromal activation. Breast cancer-derived exosomal miR-105 disrupts tight junctions (ZO-1, occludin), facilitating vascular leakiness and tumor cell extravasation.[37] Exosomal Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), A Disintegrin And Metalloproteinase 17 (ADAM17), and S100 Calcium-Binding Protein A8/A9 (S100A8/A9) activate fibroblasts and neutrophils, promoting MMP secretion and fibronectin deposition.[32,38]

Organotropism is largely dictated by exosomal surface integrins, whereby αvβ5 directs uptake by liver Kupffer cells, while α6β4 and α6β1 preferentially target lung fibroblasts and epithelial cells.[39] Pancreatic cancer exosomes induce hepatic fibronectin production and macrophage recruitment, whereas exosomal RNAs activate Toll-Like Receptor 3 (TLR3) in alveolar epithelial cells to drive lung PMN formation.[40,41] Therapy-induced stress can amplify these processes. Exosomes released after chemotherapy or radiation are enriched in Talin-1 (TLN1), which shifts the EMT/MET (MET Proto-Oncogene [Hepatocyte Growth Factor Receptor]) balance through c-Src/TGF-β1

signaling, potentially increasing metastatic dissemination.[41]

Collectively, these findings establish that exosomes are active drivers of EMT and PMN formation. By coordinating ECM remodeling, endothelial disruption, and stromal activation across distant sites, exosomes endow tumor cells with plasticity that facilitates metastatic colonization.

METABOLIC REPROGRAMMING BY TUMOR-DERIVED EXOSOMES

Glucose metabolism

Tumor exosomes actively reinforce aerobic glycolysis in surrounding stromal and immune cells, sustaining the Warburg phenotype and acidifying the microenvironment. In colorectal cancer, exosomes elevate Glucose Transporter 1 (SLC2A1) (GLUT1) while suppressing caveolin-1, driving glucose uptake and glycolytic enzyme activation.[42] Melanoma exosomes enriched in miR-155 and miR-210 similarly support glycolytic gene expression, promoting lactate buildup and ECM acidification.[43]

Immune metabolism

Exosomes also reshape immune cell metabolism to favor immune suppression. Melanoma-derived vesicles push macrophages toward an M2-like, glycolysis-dependent state via TLR2/NF-κB signaling while reducing Oxidative Phosphorylation (OXPHOS).[44] Conversely, hypoxic tumor exosomes carrying let-7a inhibit insulin-AKT-mTOR signaling and enhance mitochondrial respiration in macrophages, showing their ability to adapt immune metabolism to environmental cues.[42]

Metabolic coupling in the TME

Within the TME, exosomes coordinate a metabolic "division of labor." In nasopharyngeal carcinoma, LMP1-positive exosomes induce glycolysis and autophagy in CAFs, while tumor cells increase oxidative metabolism. This establishes a lactate shuttle-CAF Monocarboxylate Transporter 4 (SLC16A3) (MCT4) to tumor MCT1-that fuels tumor growth.[45]

Systemic metabolic control

Beyond the primary tumor, exosomes reshape systemic nutrient use. Breast cancer exosomes carrying miR-122 suppress pyruvate kinase in distant tissues, lowering their glucose consumption and redirecting glucose to metastatic cells.[42,46]

Lipid metabolism

Exosomes also influence lipid utilization. Adipocyte-derived vesicles enriched in Fatty Acid Oxidation (FAO) enzymes Enoyl-CoA Hydratase, Short Chain 1 (ECHA), Hydroxyacyl-CoA Dehydrogenase Trifunctional Multienzyme Complex Subunit Alpha (HADHA) enhance fatty acid oxidation in melanoma cells, promoting invasion.[47] In contrast, HCC exosomes containing CD147 activate Sterol Regulatory Element-Binding Protein 1c (SREBP1c) and stimulate Fatty Acid Synthase (FASN) and ATP-Citrate Lyase (ACLY)-driven lipid synthesis.[43] Exosomal Dedicator of Cytokinesis 7 (DOCK7) further supports lipid accumulation and metabolic enzyme upregulation in macrophages.[48]

Amino acid metabolism

Exosomes modulate amino acid metabolism during nutrient stress. Stromal cell exosomes supply glutamate and lactate to breast cancer cells to support the Tricarboxylic Acid Cycle (Krebs Cycle) (TCA) cycle.[43] The CAF-derived vesicles deliver glutamine and Long Intergenic Non-Protein Coding RNA 1614 (LINC01614), enhancing NF-κB activity and amino acid transporter expression. Esophageal cancer exosomes carrying circular RNA derived from SFMBT2 gene (circ-SFMBT2) increase Solute carrier family 1 member 5 (SLC1A5), also known as the glutamine transporter ASCT2 by sponging miR-107.[43] Under hypoxia, tumor cells reroute CAF-derived glutamine toward reductive carboxylation to sustain lipid synthesis.

Overall, tumor and stromal exosomes serve as metabolic regulators that reshape glycolysis, mitochondrial activity, and nutrient flow, establishing a microenvironment that supports tumor growth, adaptation, and metastasis.[46,47]

THERAPY RESISTANCE: EXOSOME-MEDIATED MECHANISMS

Exosomes are crucial agents of therapy resistance, conveying bioactive molecules

that alter the TME and enhance intercellular communication. By transferring miRNAs, lncRNAs, circRNAs, proteins, lipids, and metabolites, they reprogram gene expression to suppress apoptosis, enhance DNA repair, promote drug efflux, and enrich EMT and cancer stem cell phenotypes.[49] This creates a "resistance ecology" in which resistant clones educate neighboring cells. Understanding exosomal cargo and behavior after metabolic reprogramming is crucial for developing strategies to overcome drug resistance.

Molecular mechanisms of exosome-mediated drug resistance

Non-coding RNAs

Exosomal non-coding RNAs (ncRNAs)-comprising miRNAs, lncRNAs, and circRNAs-facilitate therapy resistance by regulating gene expression, inhibiting apoptosis, and stimulating survival pathways such as PI3K/AKT, MAPK/ERK, and NF-κB.[49,50] MicroRNAs, including miR-221/222, miR-21, and miR-100-5p, augment resistance to tamoxifen, paclitaxel, and cisplatin by inhibiting tumor suppressors. Long non-coding RNAs, such as lncARSR, lncH19, MALAT1, and UCA1, facilitate EMT, confer cancer stem cell characteristics, and induce resistance to tyrosine kinase inhibitors through miRNA sponging. Circular RNAs, such as circRNA-Stress-Induced Oncogenic Reprogramming Element (SORE), circNFIX, and circHIPK3, modulate protein stability and miRNA availability to augment chemoresistance.[51-54]

Exosomal proteins and drug efflux

Exosomal proteins, such as P-glycoprotein (P-gp/ABCB1), Multidrug Resistance-Associated Protein 1 (MRP1, ABCC1), survivin, heat shock protein 70 (HSP70), Bcl-2, and HIF-1α, facilitate multidrug resistance through mechanisms including drug efflux, sequestration of chemotherapeutics, inhibition of apoptosis, and stabilization of pro-survival signaling.[55] In addition, TDEs may encapsulate and sequester chemotherapeutic agents, subsequently exporting them into the extracellular milieu. This process reduces intracellular drug accumulation, diminishes cytotoxic efficacy, and facilitates the horizontal propagation of resistance phenotypes within the TME. Collectively, these findings highlight exosome-mediated drug efflux as a pivotal mechanism by which cancer cells maintain survival under chemotherapeutic pressure.

Apoptosis evasion and DNA repair

Exosomal proteins such as survivin, HSP70, Bcl-2, and HIF-1α play crucial roles in enhancing cellular survival under therapeutic stress by suppressing apoptosis and stabilizing pro-survival signaling networks. Proteins like survivin and HSP70 inhibit apoptosis, whereas ncRNAs modulate DNA repair genes such as Poly (ADP-Ribose) Polymerase 1 (PARP1) and Excision Repair Cross-Complementation Group 1 (ERCC1), thereby enhancing the DNA damage response and diminishing the effectiveness of agents like cisplatin and etoposide.[56] Concurrently, exosomal ncRNAs cargos further reinforce this resistance by modulating the expression of DNA repair genes, including PARP1 and ERCC1, thereby strengthening the DNA damage repair machinery. These cooperative alterations collectively attenuate the cytotoxic effects of DNA-damaging agents such as cisplatin and etoposide, reducing treatment efficacy and promoting long-term survival of resistant clones.[56] The study demonstrated that survivin is actively secreted from cancer cells through exosomes, suggesting that exosomal survivin contributes to apoptosis inhibition and may serve as a mechanism for enhanced tumor cell survival and therapy resistance.

Crosstalk with the tumor microenvironment and immune evasion

Stromal cell-derived exosomes, particularly those secreted by CAFs and M2-polarized macrophages, play an active role in sustaining drug resistance and shaping an adaptive TME. The CAF-derived vesicles enriched in TGF-β, IL-6, and miR-92a-3p promote EMT, activate anti-apoptotic signaling, and enhance survival under chemotherapeutic stress. The study concluded that CAF-derived exosomes promote metastasis and chemotherapy resistance in colorectal cancer by enhancing cancer cell stemness and inducing EMT, thereby facilitating tumor progression and therapeutic failure.[57] Exosomes derived from M2 macrophages, which

contain miR-21-5p and miR-223, enhance chemoresistance by inhibiting Phosphatase and Tensin Homolog (PTEN) and activating the PI3K/AKT pathway.[58] Under hypoxic conditions, HIF-1α-enriched exosomes reconfigure tumor metabolism, enhancing oxidative stress tolerance and metabolic plasticity.[52] Tumor-derived exosomal PD-L1 diminishes T-cell cytotoxicity, undermining the effectiveness of checkpoint blockade. Exosomes inhibit NK-cell activity, impede dendritic cell maturation, and modify macrophage polarization, thereby creating an immunosuppressive TME.[59]

Clinical implications and therapeutic perspectives

Exosomal ncRNAs, such as miR-221/222, lncARSR, and circRNA-SORE, exhibit stability in biological fluids and present potential as liquid biopsy biomarkers for the early identification of therapy resistance and treatment assessment.[60]

Therapeutic approaches that target exosomes include:

1. Suppression of exosome biogenesis or internalization (e.g., GW4869, nSMase2 inhibitors).[61]
2. Engineered exosomes administering anti-miR or anti-lncRNA therapeutics, successfully reversing chemoresistance.[62,63]
3. Exosomes derived from MSCs, which contain tumor-suppressive miRNAs like miR-34a and miR-16, downregulate oncogenes (BCL2, MET) and restore drug sensitivity.[64]

Exosomal miRNAs, including miR-21, miR-155, and miR-375, actively regulate oncogenic pathways (PI3K/AKT, MAPK/ERK, MYCN Proto-Oncogene, bHLH Transcription Factor [MYCN]), enhance proliferation, angiogenesis, and immune evasion, and function as biomarkers and therapeutic targets in aggressive cancers.[65]

In conclusion, the evidence shows that exosome proteins play a key role in the growth and spread of cancer cells. They do this by helping the cells to adapt to changes in their environment, change their function, avoid being attacked by the immune system, and resist treatment. By moving proteins, non-coding RNAs, and metabolites around, they change the tumour microenvironment, encourage a process called EMT and the formation of a pre-metastatic niche, and quickly spread resistance mechanisms that stop chemotherapy and immunotherapy from working. Beyond these well-known roles, this review shows how exosome-mediated signaling may work at a higher level, coordinating metabolic programmes such as glutamine acquisition and spreading shared antioxidant and redox adaptations that allow tumours to survive under stress from treatment. These findings suggest that networks of exosomes not only show how tumours are changing, but also actively coordinate ways to deal with them in different parts of the tumour and the surrounding tissue. So, focusing on how exosome biogenesis, release, uptake, and specific metabolic and redox cargo work is a really exciting area for precision oncology. This could lead to liquid biopsy biomarkers that can predict treatment outcomes and make tumours more sensitive to both conventional and immune-based therapies.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: I.Y.C., A.A.: Contributed substantially to the conception and design of the review. I.YC, A.A, N.E, I.C.: The literature search and selection were performed collaboratively by all authors. Data collection, analysis, and interpretation of the relevant studies were carried out jointly. All authors participated in the critical evaluation and synthesis of the literature. The manuscript was written collectively, and all authors contributed to drafting and revising the article critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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