

Molecular mechanisms of exosome-mediated drug resistance in central nervous system tumours

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ABSTRACT

Exosomes are 30–150 nm extracellular vesicles released via fusion of multivesicular bodies with the plasma membrane and enriched in selectively sorted proteins, lipids and nucleic acids that reflect both donor-cell state and regulated packaging pathways. In central nervous system (CNS) tumours, exosome-mediated communication is increasingly recognised as a scalable mechanism by which malignant cells coordinate adaptation to therapy across cellular and anatomical barriers, including the blood–brain barrier. This review synthesises current evidence linking exosome biogenesis and cargo selection (ESCRT-associated factors, tetraspanins, Rab GTPases, RNA-binding proteins) with key resistance phenotypes in glioblastoma and other CNS tumour entities. We outline four convergent routes by which exosomes blunt therapeutic efficacy: horizontal transfer of resistance determinants, rapid activation of pro-survival signalling hubs, tumour-microenvironment remodeling, vesicle-enabled “drug scavenging”, where cytotoxic agents and/or efflux machinery are sequestered and exported, lowering effective intracellular drug exposure. Finally, we discuss translational opportunities and constraints, highlighting exosome-based liquid biopsy strategies in CSF and blood and therapeutic concepts targeting vesicle biogenesis, release or uptake, while emphasizing the need for rigorous EV characterization and reporting standards to accelerate clinical implementation.

1. Introduction

Interest in exosome-mediated therapeutic resistance in CNS tumours has expanded rapidly: a focused search of PubMed-indexed literature conducted on 3 August 2026 identified 65 journal articles published during the preceding three years (3 August 2023–3 August 2026) that linked exosomes or extracellular vesicles with drug, chemo-, radio-, or

therapy resistance in CNS tumour models. Central nervous system (CNS) tumours remain among the most treatment-refractory malignancies, not only because of their intrinsic aggressiveness, but because therapeutic pressure is met by rapid, coordinated adaptation across malignant and non-malignant compartments (Parikh and Sait, 2025). Clinical relapse is often driven by residual disease that survives initial debulking and chemoradiotherapy, then re-expands within a microenvironment

Abbreviations: BBB, blood–brain barrier; BMP, bismonoacylglycerophosphate; Cav-1, caveolin-1; Cer, ceramides; CircRNAs, circular RNAs; CNS, Central nervous system; CSF, cerebrospinal fluid; DAG, Diacylglycerols; DAs, dopamine agonists; ECM, extracellular matrix; EEs, early endosomes; ESCRT, endosomal sorting complex required for transport; EVs, extracellular vesicles; H3K27M-pDMG, H3K27M-mutant diffuse midline gliomas; IDE, insulin-degrading enzyme; ILV, intraluminal vesicle; LBPA, lysobisphosphatidic acid; LLPS, liquid–liquid phase separation; LPC, lysophosphatidylcholine; MDSCs, myeloid-derived suppressor cells; MIF, macrophage migration inhibitory factor; MT1-MMP, membrane-type 1 matrix metalloproteinase; MVBs, multivesicular bodies; NSMase, Neutral sphingomyelinase; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositols; PNF1, plexiform neurofibroma; PS, phosphatidylserine; RBPs, RNA-binding proteins; SEVs, small extracellular vesicles; SM, sphingomyelin; TAG, triacylglycerols; TMZ, temozolomide; TAM, tumor-associated macrophage; TME, tumor microenvironment; Vps, vacuolar protein sorting.

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shaped by hypoxia, inflammatory signalling, altered metabolism, and limited drug exposure. In this setting, resistance cannot be understood solely as a cell-autonomous trait emerging from clonal selection; it also reflects a distributed systems response in which information, resources and protective programs are exchanged between cells. Exosome-enriched small extracellular vesicles have emerged as a compelling mechanism for this coordination (Isik et al., 2025). Generated through the endosomal pathway and released upon fusion of multivesicular bodies with the plasma membrane, these vesicles carry selectively packaged proteins, lipids and nucleic acids that can remodel gene expression and signalling states in recipient cells. Importantly, vesicle cargo is shaped by regulated sorting rather than passive leakage, enabling tumours to broadcast phenotype, stress tolerance, therapy evasion, and niche conditioning well beyond the cells in which these programs first arise (Wang et al., 2024a). In CNS tumours, this communication layer intersects with uniquely practical constraints, including blood-brain barrier-limited pharmacokinetics, spatial heterogeneity, and the availability of cerebrospinal fluid (CSF) as a clinically relevant reservoir of tumour-derived vesicles (Seyhan, 2024). The unmet clinical need is acute: in glioblastoma, only approximately 10% of patients respond to standard-of-care therapies and the 5-year survival rate is 6.8%; translation of EV-based biomarkers is further constrained by non-standardised sample collection and analyte isolation, heterogeneous analytical workflows, small cohorts, and limited prospective validation (Seyhan, 2024). Pharmacological blockade of exosome biogenesis also remains preclinical, and widely used inhibitors such as GW4869 lack the solubility and inhibitory potency required for further clinical development (Han et al., 2022).

In this review, we synthesise mechanistic evidence positioning sEVs as a scalable resistance system in CNS tumours, with emphasis on glioblastoma as the best-characterised model. We organise the field around four convergent routes by which vesicles can blunt therapeutic efficacy: horizontal transfer of resistance determinants, rewiring of pro-survival signalling and shifting of apoptotic thresholds through recurrent nodes such as PI3K/AKT and MAPK/ERK; microenvironmental reprogramming, including immunosuppressive myeloid education, angiogenic plasticity, and extracellular-matrix changes that jointly sustain residual disease and restrict effective drug penetration; and vesicle-enabled pharmacologic buffering, in which drugs and/or drug-handling machinery are sequestered and exported, lowering intracellular exposure. These converging trends, the expanding evidence base, persistent therapeutic failure, and unresolved translational barriers, provide the rationale for this focused review of the molecular mechanisms by which exosomes propagate drug resistance in CNS tumours.

1.1. Methodology of literature search and evidence synthesis

This narrative review was informed by a structured, topic-focused search of PubMed/MEDLINE. Search terms were organised around three principal concepts: extracellular vesicles, CNS tumour entities and therapeutic resistance. The search included combinations of terms such as “exosome”, “extracellular vesicle”, “small extracellular vesicle”, “glioma”, “glioblastoma”, “medulloblastoma”, “ependymoma”, “meningioma”, “schwannoma”, “diffuse midline glioma”, “primary CNS lymphoma”, “brain metastasis”, “drug resistance”, “chemoresistance”, “radioresistance” and “therapy resistance”. Reference lists of relevant original studies, reviews and consensus statements were additionally screened to identify historical, methodological and mechanistic publications. Original *in vitro*, *ex vivo*, *in vivo*, translational and clinical studies addressing EV-mediated therapeutic resistance, treatment adaptation or altered drug exposure in CNS tumours were prioritised. Reviews and consensus statements were used to provide historical, methodological and conceptual context. Evidence from non-CNS tumour models was included only when it addressed mechanisms for which direct CNS-tumour evidence was unavailable and was explicitly identified as indirect or supportive. Studies were selected according to their

relevance to CNS tumours, mechanistic specificity, cargo-directed perturbation, functional validation and recency. Because of substantial heterogeneity in tumour entities, therapeutic settings, EV isolation and characterisation methods, experimental models and reported outcomes, the evidence was synthesised narratively. No meta-analysis or formal risk-of-bias assessment was performed.

2. The composition of exosomes

Exosomes are extracellular vesicles, 30–150 nm in diameter, released through the fusion of multivesicular bodies (MVBs) with the plasma membrane (Han et al., 2022). Exosomes carry a complex and selectively enriched cargo that represents both donor-cell characteristics and regulated packaging pathways. Their contents encompass surface-bound and intraluminal proteins, lipids, and nucleic acids, including DNA, mRNA, and miRNA (Mashouri et al., 2019). Emerging evidence suggests that although the exosome classes display some common properties, they are largely distinguished by differences in cargo composition and biogenetic pathways (Han et al., 2022).

2.1. The composition of exosomes – proteins

Exosomes have attracted considerable attention as biologically derived platforms for protein-based therapeutics (Li et al., 2023). Extracellular vesicles contain a limited protein load, typically comprising fewer than 100 distinct proteins per vesicle, with approximately 1 µg of total protein obtainable from 10^9 – 10^{10} EVs. Despite marked heterogeneity in protein composition among vesicles of the same class, specific proteins are consistently detected within particular EV subtypes, consistent with their roles in vesicle formation and selective cargo incorporation (Lai et al., 2022).

Proteins are incorporated into exosomes through multiple sorting mechanisms. Many are directed to multivesicular bodies via interactions with ESCRT-dependent or ESCRT-independent pathways. Certain cargos, particularly cytoplasmic proteins, are selectively packaged into intraluminal vesicles and subsequently into exosomes (Lai et al., 2022).

Exosomal protein composition reflects their biogenesis pathways. Because exosome formation and multivesicular body (MVB) trafficking are to a great extent regulated by the ESCRT machinery, ESCRT components and closely associated proteins, such as syntenin-1, ALIX, TSG101, HSC70, and HSP90 β , are frequently detected in exosomes and are widely regarded as canonical exosomal markers. Proteins including ALIX, flotillin, and TSG101 directly contribute to exosome biogenesis, while exosomal membranes are often enriched in tetraspanins (CD63, CD9, CD81). Although tetraspanins are not strictly exosome-specific, they play important roles in membrane fusion, signaling, and protein trafficking. In general, exosomes are enriched in ESCRT-associated factors that mediate MVB and intraluminal vesicle (ILV) formation, as well as Rab27a and annexins that regulate vesicle docking and secretion; they also commonly contain cytoskeletal proteins (e.g., actin and myosin) and heat shock proteins (Hsp70, Hsp90) (Lai et al., 2022; Doyle and Wang, 2019). The major exosomal proteins discussed above, together with their principal functions in EV biogenesis, trafficking, cargo sorting, membrane organization, and intercellular communication, are summarized in Table 1.

Selective RNA cargo loading is likewise tightly regulated by RNA-binding proteins (RBPs) that mediate miRNA sorting into exosomes. YBX1 can recognize specific sequence motifs, whereas Ago2, a core component of the RISC complex, coordinates miRNA loading through interactions with other RBPs and with the ESCRT machinery. Moreover, the secondary structure of miRNA duplexes influences Ago2-dependent incorporation, mechanistically linking RNA processing to MVB formation and exosome biogenesis (Lai et al., 2022).

From an applied perspective, several exosomal membrane proteins represent potential targets for immunoaffinity isolation, including SLC1A5, CD47, ATP1A1, SLC3A2, ITGB1, and BSG. CD47, which is often

Table 1
Composition of exosomes: main proteins and functions.

Proteins	Function / Role in Exosomes
Hrs, ALIX, TSG101, Flotillin, Syntenin-1	Mediate MVB and ILV formation; contribute to exosome biogenesis; canonical exosomal markers
Rab27a, Annexins	Regulate MVB docking and exosome secretion
CD9, CD63, CD81	Enriched in exosomal membranes; involved in membrane fusion, signaling, and protein trafficking
CD47, ITGB1, SLC1A5, ATP1A1, SLC3A2, BSG	Membrane proteins; mediate phagocytosis evasion (CD47), cell targeting/metastasis (ITGB1), adhesion/internalization (BSG), and ion/amino acid transport (ATP1A1, SLC1A5, SLC3A2)
LGALS3BP	Binds ITGB1, collagen, fibronectin; promotes adhesion and internalization of exosomes
Actin, Myosin	Provide structural support; maintain vesicle integrity
Hsp70, Hsp90	Chaperones; assist protein folding; stress response; exosomal cargo
HMGB1, HMGB2, HMGB3	Nuclear proteins excluded from exosomes; prevent triggering host immune responses via TLRs and RAGE
YBX1, Ago2	RNA-binding proteins; mediate selective miRNA sorting into exosomes via sequence/structural recognition and interactions with ESCRT machinery
MT1-MMP, IDE, Sialidase, Heparanase	Surface-associated enzymes; retain catalytic activity; mediate growth factor mobilization, extracellular matrix degradation, and amyloid β clearance

enriched in exosomes, may protect them from phagocytosis by leveraging the “don’t eat me” signal. Exosomal ITGB1 has been implicated in cell targeting and metastatic niche formation, while LGALS3BP may promote adhesion and internalization through interactions with ITGB1, collagen, and fibronectin. The presence of ATP1A1 and the amino-acid transporters SLC1A5 and SLC3A2 further suggests roles for ion and amino-acid transport across the exosomal membrane. Notably, some proteins appear to be excluded from exosomes, including nuclear HMGB1, HMGB2, and HMGB3, potentially helping to prevent activation of host immune responses via TLRs and RAGE (Huang et al., 2025; Kugerski et al., 2021).

Recent studies have identified several enzymes, including membrane-type 1 matrix metalloproteinase (MT1-MMP), insulin-degrading enzyme (IDE), sialidase, and heparanase, on the surface of exosomes derived from diverse cell types. These surface-associated enzymes retain catalytic activity and can process their physiological substrates in the extracellular environment. Functionally, exosomal enzymes have been implicated in growth factor mobilization, extracellular matrix remodeling, and the clearance of amyloid β aggregates (Sanderson et al., 2019).

Exosomes are typically enriched in glycoproteins relative to parental cells. Proteins associated with organelles such as mitochondria, nucleus, Golgi apparatus, and endoplasmic reticulum are generally considered non-exosomal markers, although low levels may be detected, reflecting interorganelle trafficking and endosomal interactions (Doyle and Wang, 2019).

2.2. The composition of exosomes – lipids

Lipids are a fundamental component of exosomes, not only providing structural integrity and maintaining vesicle shape but also playing active roles in biogenesis and in regulating homeostasis in recipient cells. High concentrations of lipids such as lysobisphosphatidic acid (LBPA) within the intraluminal membranes of MVBs interact with Alix to promote MVB budding and facilitate the formation of intraluminal vesicles (ILVs).

Other lipids, including phosphatidylcholine (PC), bis(monoacylglycerol) phosphate (BMP), and sphingomyelin (SM), contribute to the differentiation and maturation of various vesicle types. Exosomal membranes are characteristically enriched in cholesterol, sphingomyelin (SM), glycosphingolipids, and phosphatidylserine (PS). Classes of lipids found in exosomes include:

- 1) Sphingolipids such as ceramides (Cer), sphingomyelins (SM), and gangliosides GM3;
- 2) Phospholipids including phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylcholine (PC), lysophosphatidylcholine (LPC), and phosphatidylinositols (PI);
- 3) Diacylglycerols (DAG), triacylglycerols (TAG);
- 4) Cholesterol (Li et al., 2023).

Beyond their structural role, these lipids actively participate in exosome formation, membrane curvature, cargo sorting, and the regulation of vesicle release. Neutral sphingomyelinase (nSMase), which converts SM into Cer, is critical for generating the intraluminal membranes of MVBs and is essential for exosome biogenesis, particularly through endosomal sorting complex required for transport (ESCRT)-independent pathways (Skotland et al., 2019). Studies have demonstrated that exosome uptake by recipient cells can alter their lipid composition, particularly cholesterol and sphingomyelin levels. These changes may consequently modulate cellular homeostasis (Mashouri et al., 2019).

2.3. The composition of exosomes – RNA

In terms of exosomal composition, RNA is a major cargo class that is selectively enriched rather than randomly incorporated. Exosomes contain a broad repertoire of nucleic acids, including mRNA, miRNA, siRNA and circular RNAs (circRNAs). This nucleic-acid cargo is shaped by sequence-specific RBPs that mediate sorting into MVBs and ILVs: several RBPs have been implicated in miRNA loading (e.g., hnRNP2B1, hnRNP1, YBX1, MVP, MEX3C, SYNCRIP, Ago2 and FMR1), whereas hnRNP2B1/hnRNP1 have been linked to loading of specific lncRNAs and hnRNP2B1 together with the ESCRT-II subunit SNF8 has been associated with circRNA sorting. Even though these factors are repeatedly observed across models, how predominantly nuclear RBPs are recruited to MVB membranes and incorporated into ILVs remains incompletely understood. Emerging evidence suggests that liquid–liquid phase separation (LLPS) may contribute to exosomal RNA composition by concentrating RBPs and their bound RNAs into condensates; for example, YBX1 forms LLPS-dependent condensates that selectively recruit miR-223 for ceramide-dependent sorting into exosomes, and disrupting YBX1 phase separation inhibits this process. Importantly, the RNA-rich composition of exosomes also underpins their translational potential: they are considered attractive mRNA delivery vehicles due to their biocompatibility, favorable bioavailability, and ability to cross the blood–brain barrier (BBB) (Han et al., 2022; Li et al., 2023).

2.4. The composition of exosomes – DNA

DNA has been reported as an additional but still debated cargo. Some studies suggest that extracellular DNA release occurs largely through exosome-independent mechanisms, whereas others support the presence of genomic DNA and nuclear proteins within ILVs/exosomes. In cancer cells, micronuclei containing genomic DNA may associate with tetraspanins, promoting their incorporation into ILVs and exosomal release. Exosomes have also been shown to carry mitochondrial DNA, potentially linking exosomal DNA cargo to mitochondrial damage and MVB–mitochondria interactions. However, the precise machinery that

transfers DNA into ILVs, whether ESCRT-dependent or via alternative pathways, and the overall contribution of exosomes to extracellular DNA secretion remain incompletely defined (Han et al., 2022).

3. Mechanisms of exosome biogenesis in tumours

Exosome biogenesis is a multistep cellular process. Proteins and lipids destined for exosomes are synthesized and processed in the endoplasmic reticulum and Golgi apparatus.

- 1) Endocytosis gives rise to early endosomes (EEs), which then mature into late endosomes. EE biogenesis begins when primary endocytic vesicles fuse, allowing newly internalized cargoes to mix and exchange membrane components through clathrin- or caveolin-dependent, as well as independent, routes (Mashouri et al., 2019).
- 2) As EEs mature, inward budding of the endosomal membrane produces intraluminal vesicles (ILVs) enriched in selected lipids, proteins, and nucleic acids. ILV formation is mainly regulated by the ESCRT machinery and associated proteins such as ALIX and TSG101, which recognize ubiquitinated membrane proteins and drive inward budding of the MVB membrane. ESCRTs are composed of class E vacuolar protein sorting (Vps) proteins that assemble into four distinct complexes: ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III (Krylova and Feng, 2023). ILVs can also form through an ESCRT-independent pathway involving ceramide-rich lipid raft microdomains that promote membrane invagination (Lai et al., 2022).
- 3) Their progressive accumulation results in MVBs. MVBs are trafficked to the plasma membrane along cytoskeletal and microtubule networks and can undergo exocytosis after fusion with the cell surface, resulting in the release of ILVs as exosomes, whereas other MVBs are targeted for degradation through fusion with lysosomes directly or via fusion with autophagosomes, followed by lysosomal delivery (Wang et al., 2024b).
- 4) Fusion of MVBs with the plasma membrane results in the release of these vesicles into the extracellular space as exosomes, carrying bioactive molecules such as mRNA and miRNA. Exosome release occurs through either a constitutive pathway involving the trans-Golgi network or a regulated pathway requiring fusion of multi-vesicular bodies with the plasma membrane. This process is controlled by Rab GTPases, particularly Rab27a and Rab27b, which mediate MVB docking, while membrane fusion is facilitated by SNARE proteins (Lai et al., 2022).
- 5) Once an exosome arrives at a recipient cell, it can influence it in three main ways: it may bind directly to cell-surface receptors via proteins on the exosomal membrane, merge with the plasma membrane, or be internalized through uptake pathways such as phagocytosis, macropinocytosis, or lipid raft-, clathrin-, or caveolin-mediated endocytosis (Krylova and Feng, 2023).

Tumor cells release higher levels of exosomes than normal cells as a result of uncontrolled proliferation and enhanced intercellular communication. Hypoxic conditions within the tumor microenvironment further stimulate the production and secretion of tumor-derived exosomes (Wang et al., 2024b).

4. Role of exosomes in cellular communication

Cell-cell communication is fundamental to the maintenance of homeostasis, enabling rapid and coordinated responses to changes or challenges in the cellular environment. In addition to traditional mechanisms involving direct cell contact and soluble messengers such as cytokines, inflammatory mediators, metabolites and hormones, cells also communicate by releasing extracellular vesicles (EVs), which serve as important carriers of intercellular signals (Pitt et al., 2016).

EVs can communicate with target cells located nearby or at distant

sites via receptor-ligand interactions at the cell surface and/or direct fusion with the plasma membrane. Most commonly, these interactions trigger EV internalization through endocytosis. Cell-to-cell communication can occur through the transfer of biological signals, primarily proteins and RNAs, via extracellular vesicles. In this process, vesicles such as exosomes released by a donor cell are taken up by recipient cells, enabling the delivery of their molecular cargo (Meldolesi, 2018). Following uptake, EV membrane components may be incorporated into the recipient cell membrane, while the vesicular cargo can be released into the cytoplasm and, in some cases, reach the nucleus. By supplying additional bioactive molecules, EVs can engage new signaling routes and elicit a wide spectrum of functional effects in recipient cells (Pitt et al., 2016).

Through these mechanisms, exosomes can modulate a wide range of biological pathways. To further develop the main theme, the next section analyses the contribution of exosomes to drug resistance, focusing on central nervous system tumors.

5. Mechanisms of EV-mediated therapy resistance

Therapeutic and microenvironmental stressors can modify EV biogenesis, cargo sorting, and release before these vesicles act on recipient cells. Temozolomide exposure, irradiation, and hypoxia may generate stress-conditioned EV populations through changes in RNA loading, ceramide-dependent ILV formation, MVB fate, and vesicle secretion. These upstream adaptations provide the mechanistic basis for the resistance pathways discussed in Sections 5.1–5.5 (Fig. 1).

5.1. Horizontal transfer of resistance determinants

Exosomes enable the horizontal transfer of drug-resistance determinants by shuttling functional mRNAs, miRNAs, lncRNAs, and proteins from resistant tumour or stromal donor cells to therapy-sensitive recipient cells, where the delivered cargo can be translated, suppress endogenous targets, or reprogramme gene expression and signalling. This process therefore allows an adaptive phenotype generated in a selected subpopulation to spread without requiring the recipient cells to acquire the same genetic alterations. However, the demonstration of functional cargo transfer does not by itself establish how a particular molecule is selected for exosomal loading, and the upstream sorting mechanisms remain undefined in many resistance models (Skog et al., 2008; Valadi et al., 2007).

In glioblastoma, this mechanism is well illustrated by temozolomide (TMZ) resistance: TMZ-resistant cells release exosomes enriched in miR-1238, and uptake of these vesicles by TMZ-sensitive cells is sufficient to *spread* resistance in vitro and in vivo (Yin et al., 2019). At the molecular level, miR-1238 directly suppresses caveolin-1 (CAV1), thereby relieving CAV1-associated restraint on epidermal growth factor receptor (EGFR) signalling and increasing the activity of downstream survival programmes. Loss-of-function experiments showed that reducing miR-1238 sensitized resistant cells to TMZ, supporting a causal rather than exclusively correlative role for the miR-1238/CAV1/EGFR axis. Nevertheless, the molecular machinery responsible for preferential enrichment of miR-1238 in resistant-cell exosomes was not identified, leaving the connection between TMZ-induced cellular stress and selective cargo loading unresolved (Yin et al., 2019).

A complementary example involves the tumour microenvironment: M2 glioblastoma-associated macrophages secrete miR-21-enriched exosomes that increase TMZ resistance and reinforce stemness-associated programs in GBM cells, linking stromal exosomal miRNA transfer to therapy failure (Chuang et al., 2019).

In recipient cells, miR-21 suppresses the tumour-suppressive programme associated with PDCD4 and reinforces STAT3-, SOX2-, and Nestin-linked stemness. The resulting increase in IL-6 and TGF- β 1 secretion can, in turn, sustain M2 macrophage polarization, creating a bidirectional positive-feedback loop in which macrophage-derived

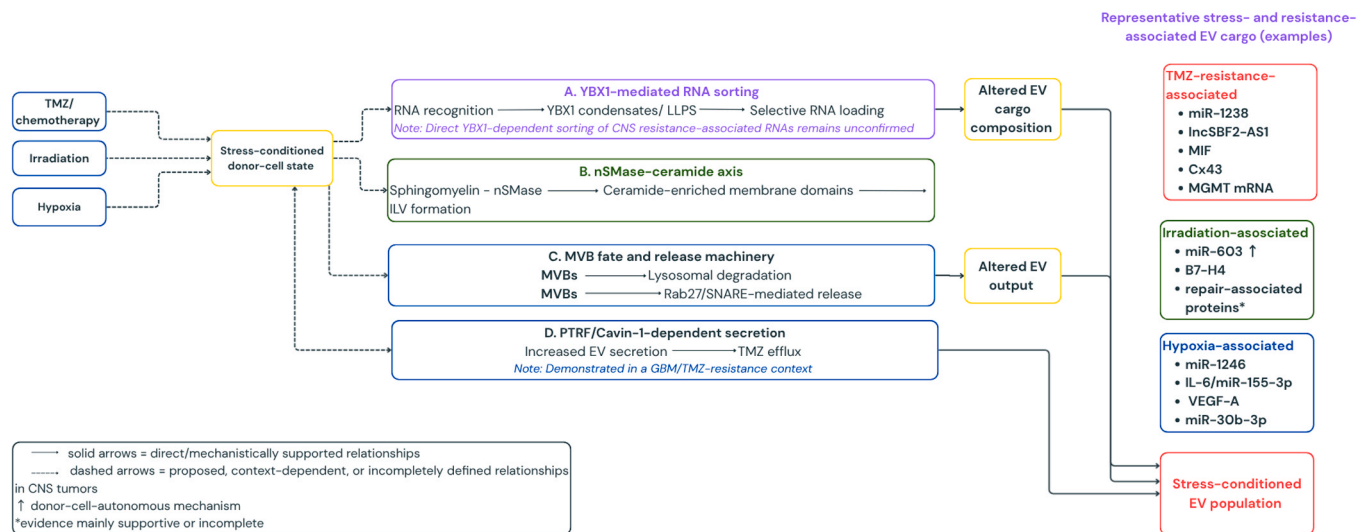


Fig. 1. Stress-Induced Remodeling of Extracellular Vesicle Biogenesis and Cargo Composition in Glioma Therapy Resistance.

exosomes increase tumour-cell resistance, while tumour-derived signals maintain the exosome-producing M2 state. Pharmacological inhibition of STAT3 with pacritinib reduced the release of miR-21-enriched macrophage exosomes and restored TMZ responsiveness in patient-derived xenograft models, providing evidence that the upstream macrophage state and exosomal output are functionally connected. Independently, miR-21 can reduce the Bax/Bcl-2 ratio and caspase-3 activity during TMZ exposure, shifting the apoptotic threshold of recipient cells away from drug-induced cell death (Chuang et al., 2019; Shi et al., 2010).

Beyond miRNAs, exosomes can disseminate resistance by restoring DNA-repair functions that are absent or insufficient in recipient cells. Glioma cells can induce a reactive phenotype in surrounding astrocytes through non-contact signalling, after which reactive astrocytes release exosomes enriched in O⁶-methylguanine-DNA methyltransferase (MGMT) mRNA. Following uptake by glioma cells, the transferred transcript is translated into functional MGMT protein, allowing removal of TMZ-induced O⁶-methylguanine lesions before they produce lethal replication-associated DNA damage. Thus, the recipient cell does not merely activate an endogenous signalling pathway; it temporarily acquires an additional DNA-repair template from a stromal compartment. Although this study directly demonstrated translation of the transferred transcript and development of a TMZ-resistant phenotype, the signals controlling MGMT mRNA enrichment within reactive astrocyte exosomes remain incompletely defined (Yu et al., 2018).

Exosome-borne lncRNAs provide a further layer of repair-driven resistance. In TMZ-resistant GBM cells, the transcription factor ZEB1 binds the promoter of lncSBF2-AS1 and increases its expression, providing an upstream regulatory connection between the resistant cellular state and the abundance of this cargo. Following exosomal transfer to sensitive cells, lncSBF2-AS1 functions as a competing endogenous RNA for miR-151a-3p, thereby releasing XRCC4 from miRNA-mediated repression. Increased XRCC4 strengthens non-homologous end joining and accelerates repair of TMZ-associated DNA double-strand breaks. Inhibition of lncSBF2-AS1 sensitized resistant cells, whereas its exosomal transfer reproduced resistance in recipient cells and intracranial xenografts. Moreover, elevated serum exosomal lncSBF2-AS1 was associated with an unfavourable response to TMZ in patients. This ZEB1-lncSBF2-AS1-miR-151a-3p-XRCC4 axis therefore provides a relatively complete mechanistic chain extending from transcriptional regulation in the donor cell through exosomal transfer to DNA-repair enhancement in the recipient cell (Zhang et al., 2019).

5.2. Convergence on pro-survival signalling and apoptosis avoidance

Exosome-mediated resistance frequently reflects rapid, non-genetic rewiring of signalling networks rather than the transfer of a single autonomous “resistance gene”. Different exosomal cargos can converge on recurrent regulatory hubs, particularly PI3K/AKT, MAPK/ERK, EGFR, and inflammatory STAT3/NF-κB signalling. Activation of these hubs simultaneously promotes proliferation, suppresses apoptotic execution, alters cellular metabolism, and maintains stem-like states, enabling recipient cells to survive long enough to repair therapy-induced damage. Importantly, pathway activation should be interpreted as a network-level response: the same exosomal cargo may influence several downstream branches, while distinct cargos can converge on the same survival node (Cela et al., 2024; Guo et al., 2025).

The miR-1238/CAV1/EGFR axis illustrates this convergence. By suppressing CAV1 in recipient cells, exosomal miR-1238 enhances EGFR-associated signalling and the downstream PI3K/AKT/mTOR pathway. This creates coordinated effects on proliferation and apoptotic resistance rather than an isolated change in a single downstream effector. The sensitization observed after miR-1238 depletion and the reproduction of resistance following transfer of resistant-cell exosomes support the functional relevance of this pathway. However, the extent to which miR-1238 acts independently of other cargos present within the same vesicle population remains uncertain (Yin et al., 2019).

TMZ-resistant glioma cells also release exosomes enriched in macrophage migration inhibitory factor (MIF). Following transfer to sensitive glioma cells, MIF suppresses tissue inhibitor of metalloproteinases 3 (TIMP3), thereby permitting sustained activation of PI3K/AKT signalling. This regulatory sequence increases proliferation and decreases apoptosis during TMZ exposure. Its causal relevance was supported by donor-cell MIF knockdown, which increased TIMP3 expression, suppressed PI3K/AKT activation, and restored TMZ sensitivity. Conversely, exosomal MIF promoted tumour growth and TMZ resistance in vivo, whereas pharmacological MIF inhibition enhanced TMZ efficacy. These experiments connect a defined alteration in donor-cell cargo with a specific recipient-cell signalling axis and an in vivo resistance phenotype (Wei et al., 2021).

Resistance can also be propagated through membrane-associated proteins that influence both vesicle uptake and recipient-cell signalling. Exosomes released by TMZ-resistant glioma cells contain increased levels of connexin-43 (Cx43) and are taken up more efficiently by sensitive cells than exosomes derived from TMZ-sensitive cells. Treatment with the Cx43-directed mimetic peptide $\sim 37,43\text{Gap}27$ reduced vesicle uptake and attenuated the increase in TMZ IC₅₀, colony formation, and

migration induced by resistant-cell exosomes. In recipient cells, Cx43-enriched vesicles increased Bcl-2 while reducing Bax and cleaved caspase-3, shifting the apoptotic balance toward survival. These findings suggest that Cx43 is not merely a transferred marker of resistant cells but may participate in vesicle–recipient interactions and subsequent anti-apoptotic reprogramming. Nevertheless, this evidence is principally derived from cultured glioma-cell models and requires confirmation in spatially complex in vivo tumours and patient-derived samples (Yang et al., 2021).

Collectively, these studies indicate that EV-mediated signalling operates as a distributed amplification system. Resistant cells can export different molecular inputs, including miRNAs, soluble signalling proteins, and membrane proteins, that converge on shared survival networks in neighbouring cells. The strongest studies include cargo-specific inhibition or pharmacological reversal; however, many experiments still use complete EV fractions, making it difficult to determine whether a single cargo is sufficient or whether resistance depends on cooperative interactions between multiple vesicular components.

5.3. EV-mediated remodelling of the tumour microenvironment

Beyond tumour cell-intrinsic rewiring, exosomes build a therapy-permissive niche by reprogramming immune, endothelial, and stromal compartments. A particularly informative example is exosomal miR-1246. Hypoxia increases miR-1246 abundance in glioma-derived exosomes through two coordinated mechanisms: POU5F1 promotes miR-1246 transcription, whereas the RNA-binding protein hnRNPA1 contributes to its selective packaging into vesicles. Following uptake, miR-1246 suppresses DUSP3 in myeloid precursor cells, resulting in sustained ERK activation and differentiation into immunosuppressive myeloid-derived suppressor cells. These cells can inhibit antitumour immune responses and allow therapy-surviving tumour populations to persist. The mechanism was supported by cargo-directed perturbation, analysis of glioma-cell- and patient-biofluid-derived exosomes, and the association between postoperative CSF exosomal miR-1246 and glioma recurrence. Nevertheless, the clinical association does not by itself prove that circulating miR-1246 is the dominant cause of recurrence, because it may also reflect the size or biological state of residual disease (Qiu et al., 2021). By expanding an immunosuppressive myeloid compartment, this pathway may reduce effective antitumour immunity and create conditions in which therapy-surviving tumour cells can persist. Hypoxia further strengthens this immunosuppressive communication. Hypoxic glioma-derived exosomes promote M2-like macrophage polarization through an IL-6–pSTAT3–miR-155–3p positive-feedback loop. This regulatory circuit is mechanistically important because the recipient macrophage is not only transiently activated but shifted toward a tumour-supportive state that can reinforce local repair, immune suppression, and tumour-cell survival (Xu et al., 2021). At the vascular interface, hypoxia-conditioned exosomal VEGF-A increases blood–brain barrier permeability by reducing the tight-junction proteins claudin-5 and occludin. Although increased permeability may appear favourable for drug entry, abnormal vascular remodelling can also contribute to heterogeneous perfusion and uneven intratumoural drug exposure. The functional consequence is therefore more complex than simple disruption of the BBB and may vary between tumour regions and therapeutic agents (Zhao et al., 2018). Glioma-derived exosomal miR-148a-3p promotes angiogenesis by inhibiting ERFF1 and activating EGFR/MAPK signalling in endothelial cells. This illustrates recipient-cell specificity: whereas EGFR/MAPK activation in tumour cells supports survival, activation of the same general signalling network in endothelial cells promotes vascular support for the tumour (Wang et al., 2020). Exosomes also interface with fibroblast-like stromal programs in CNS tumours (e.g., mesenchymal stem-like stromal cells), where tumour education promotes extracellular matrix (ECM) remodeling and a more infiltrative, treatment-refractory tissue architecture (Kim et al., 2022). Because excessive or therapy-remodeled ECM is a recognized physical and

biochemical barrier that can limit drug penetration and shelter tumour cells, exosome-driven stromal/ECM reprogramming becomes a practical mechanism of resistance at the tissue scale (Masuda, 2025; Prakash and Shaked, 2024).

EVs may additionally influence the matrix more directly. Tethered exosomes carrying MT1-MMP can concentrate proteolytic activity near the cell surface and contribute to local extracellular-matrix degradation. Such spatially restricted remodelling may facilitate invasion and increase regional heterogeneity, thereby further limiting uniform therapeutic exposure. However, the direct relevance of this specific mechanism to CNS tumours requires further validation (Palmulli et al., 2025).

5.4. Exosomes as “Drug Scavengers”

Beyond transferring resistance-associated RNAs and proteins, tumour-derived small extracellular vesicles (sEVs, including exosomes) can function as drug “scavengers” that lower the effective intracellular dose of chemotherapy by sequestering cytotoxic molecules into endosomal/MVB compartments and exporting them via vesicle release, a mechanism increasingly discussed alongside classical membrane efflux pumps (Yang et al., 2022a; Xavier et al., 2022).

In glioblastoma, PTRF/Cavin-1 enhances chemoresistance by increasing EV secretion and promoting TMZ efflux through extracellular vesicles. Increased vesicular export reduces intracellular TMZ accumulation and attenuates downstream DNA-damage responses. This connects regulation of vesicle secretion with the pharmacological availability of TMZ inside the tumour cell (Yang et al., 2022b).

EVs can also transfer components of the classical multidrug-resistance machinery. P-glycoprotein, encoded by *ABCB1*, has been detected in vesicles released by multidrug-resistant tumour cells and can be transferred to drug-sensitive cells. Following incorporation into recipient-cell membranes, functional P-glycoprotein increases drug efflux and reduces doxorubicin cytotoxicity. In this model, EVs do not merely activate transcription of an endogenous transporter but provide recipient cells with already produced efflux machinery (Xavier et al., 2022; Rigogliuso et al., 2024).

Evidence for this mechanism in CNS tumours remains less extensive. In SHH medulloblastoma models, extracellular vesicles from vincristine-tolerant cells increased vincristine resistance in sensitive cells, while *ABCB1* inhibition abolished the acquired resistant phenotype. These findings are consistent with an EV-dependent multidrug-resistance mechanism, although additional cargo-specific studies are needed to determine whether functional *ABCB1* transfer is directly responsible for the observed effect (Wade et al., 2023).

Overall, EV secretion may support resistance at two levels: by removing cytotoxic agents from the producing cell and by increasing the drug-export capacity of neighbouring cells. These mechanisms may cooperate with pro-survival and DNA-repair pathways, because even a modest reduction in intracellular drug concentration can provide additional time for repair and adaptive signalling (Yang et al., 2022a; Xavier et al., 2022).

5.5. EV-mediated radioresistance

Ionizing radiation not only induces DNA damage in directly irradiated tumour cells but also changes vesicle-mediated communication. Radiation acts as an upstream stressor that can increase EV release and modify vesicular cargo, allowing surviving cells to transmit stress-adaptive signals to neighbouring populations. In experimental models, irradiation increases exosome output, and vesicles derived from irradiated cells enhance proliferation and clonogenic survival of recipient cells following subsequent irradiation. These findings support an EV-mediated bystander response in which cellular adaptation is propagated beyond the initially irradiated population (Dong et al., 2024).

Radiation also alters EV protein composition. Proteomic analyses

have demonstrated enrichment of proteins associated with DNA-damage responses, double-strand-break repair, including XRCC5 and XRCC6, oxidative-stress regulation, and proteostasis. Such cargo may improve the ability of recipient cells to tolerate or repair radiation-induced damage. Nevertheless, enrichment of a protein within EVs does not by itself establish that it is functionally delivered or individually responsible for radioresistance (Abramowicz et al., 2019).

Functionally, irradiated-cell-derived EVs can activate ERK- and AKT-associated survival signalling, reduce apoptotic priming, and promote radiation resistance in recipient cells. These pathways can increase survival directly while also providing additional time for repair of radiation-induced lesions. However, some of this evidence originates from non-CNS tumour or neuroblastoma models and therefore supports a general regulatory principle rather than proving that all CNS tumours use identical pathways (Abramowicz et al., 2019; Tortolici et al., 2021).

More direct CNS-specific evidence is available in glioblastoma. Irradiation promotes extracellular-vesicle-mediated export of miR-603, reducing its intracellular abundance and derepressing IGF1/IGF1R signalling. This promotes a stem-like, treatment-refractory state and illustrates an important alternative mechanism: EV-mediated resistance can arise not only through delivery of oncogenic cargo to recipient cells but also through removal of a tumour-suppressive molecule from the irradiated donor cell (Ramakrishnan et al., 2020). Radiation-enhanced exosomal B7-H4 provides a complementary link between the DNA-damage response and immune escape. B7-H4-containing exosomes released by irradiated glioblastoma cells can promote local immunosuppression and support tumour outgrowth following radiotherapy. Thus, radiation-conditioned EVs may simultaneously reinforce tumour-cell survival and weaken antitumour immune responses (Tian et al., 2022).

Together, these findings support a model in which radiotherapy-induced EVs amplify resistance through coordinated dissemination of DNA-repair capacity, activation of pro-survival signalling, maintenance of stem-like states, and immune suppression. The available evidence is strongest when a defined cargo has been linked to a functional response, whereas broader proteomic changes should be interpreted as candidate regulatory networks requiring cargo-specific validation (Li et al., 2022).

5.6. Stress-responsive regulation of EV cargo selection and biogenesis

The resistance mechanisms discussed in the preceding sections describe the functional consequences of EV-mediated communication in recipient tumour and stromal cells. However, the abundance and composition of resistance-associated EVs are also influenced by regulatory processes operating within the EV-producing cell. Therapeutic and microenvironmental stress may modify the intracellular availability of candidate cargo, its recruitment into intraluminal vesicles, multivesicular-body trafficking and the amount of EVs released (Han et al., 2022; Krylova and Feng, 2023; Wang et al., 2024b). Y-box-binding protein 1 (YBX1) and the neutral sphingomyelinase–ceramide axis illustrate two complementary regulatory levels through which the state of the donor cell may influence EV cargo composition and output (Han et al., 2022; Huang et al., 2025; Skotland et al., 2019; Krylova and Feng, 2023).

5.6.1. YBX1 as a regulatory node of RNA cargo sorting

As outlined in Section 2.3, RNA cargo is selectively enriched in EVs rather than randomly incorporated. RNA-binding proteins can recognise specific RNA sequences or structures and contribute to their sorting into multivesicular bodies and intraluminal vesicles (Han et al., 2022; Huang et al., 2025). YBX1 represents an illustrative regulatory node because it can participate in selective RNA recognition and organise RNA cargo through liquid–liquid phase separation. YBX1-containing condensates can concentrate selected RNAs, while disruption of this process reduces ceramide-dependent sorting of miR-223 into EVs (Han et al., 2022; Huang et al., 2025). This mechanism provides a potential framework for

understanding how stress-associated changes in the intracellular RNA pool could affect EV composition. Therapeutic stress may alter RNA expression, stability or accessibility to RNA-binding proteins, thereby changing which transcripts are available for vesicular loading (Han et al., 2022; Huang et al., 2025). However, the available CNS-tumour studies do not yet define a complete stress–YBX1–cargo–resistance pathway. In glioblastoma models, EV-associated miR-1238 and lncSBF2-AS1 contribute to acquired TMZ resistance, whereas irradiation induces EV-mediated export of miR-603 and promotes an IGF1/IGF1R-associated stem-like state (Yin et al., 2019; Zhang et al., 2019; Ramakrishnan et al., 2020). These studies establish resistance-associated transfer or export of defined RNA cargo, but they do not demonstrate that YBX1 is the upstream sorting factor responsible for their incorporation into EVs (Yin et al., 2019; Zhang et al., 2019; Ramakrishnan et al., 2020). Accordingly, increased abundance of a transcript in EVs should not automatically be interpreted as evidence of selective YBX1-dependent loading. Such enrichment may reflect increased intracellular RNA abundance, altered RNA stability, preferential recruitment into EVs or a general increase in EV production (Han et al., 2022; Huang et al., 2025; Krylova and Feng, 2023). Distinguishing these possibilities would require parallel assessment of donor-cell RNA abundance, EV number and EV-associated cargo following YBX1 perturbation (Huang et al., 2025). YBX1 should therefore be considered a mechanistic framework for stress-responsive RNA sorting rather than a confirmed regulator of every resistance-associated RNA described in CNS tumours (Huang et al., 2025; Yin et al., 2019; Zhang et al., 2019; Ramakrishnan et al., 2020).

5.6.2. The neutral sphingomyelinase–ceramide axis as a regulatory node of EV formation

The neutral sphingomyelinase–ceramide axis operates at the level of endosomal membrane organisation and EV formation. Neutral sphingomyelinase converts sphingomyelin into ceramide, generating ceramide-enriched membrane domains that promote membrane curvature and intraluminal-vesicle formation through an ESCRT-independent mechanism (Skotland et al., 2019; Krylova and Feng, 2023). EV output is additionally influenced by multivesicular-body fate, including the balance between lysosomal degradation and trafficking towards the plasma membrane for vesicle release (Krylova and Feng, 2023). This pathway provides a potential connection between cellular stress and the scale of EV-mediated communication. Hypoxia has been associated with increased EV production and the release of vesicles that modify macrophage, endothelial and blood–brain barrier responses (Wang et al., 2024b; Xu et al., 2021; Zhao et al., 2018). Irradiation similarly alters EV release and cargo in glioblastoma, including the export of miR-603 and the release of B7-H4-containing EVs (Ramakrishnan et al., 2020; Tian et al., 2022). Chemotherapy may also affect EV trafficking, as PTRF/Cavin-1-dependent secretion promotes TMZ efflux and reduces intracellular drug exposure in glioblastoma cells (Yang et al., 2022b). Nevertheless, these observations do not demonstrate that the nSMase–ceramide axis directly controls each stress-associated EV cargo. Changes in EV composition may reflect altered intracellular cargo availability, whereas increased EV abundance may involve changes in vesicle formation, multivesicular-body trafficking or secretion (Han et al., 2022; Krylova and Feng, 2023). Stress-associated alterations in EV output should therefore not be attributed specifically to neutral sphingomyelinase activity unless this pathway has been directly assessed or perturbed. Pharmacological inhibition with GW4869 illustrates this limitation. In an experimental glioblastoma model, inhibition of neutral-sphingomyelinase-dependent EV biogenesis was associated with suppression of malignant behaviour, glucose-metabolic remodelling and restoration of TMZ sensitivity (Han et al., 2026). However, GW4869 acts on ceramide-dependent lipid pathways and should be regarded as an experimental pathway inhibitor rather than a selective inhibitor of all tumour-derived EVs (Skotland et al., 2019; Krylova and Feng, 2023; Han et al., 2026). The observed restoration of TMZ sensitivity therefore

supports the involvement of nSMase-sensitive EV biology but does not identify the specific EV population or molecular cargo responsible for the effect (Han et al., 2026). YBX1 and the nSMase–ceramide axis thus operate at distinct but potentially connected levels of EV regulation. YBX1 influences the recognition and availability of candidate RNA cargo, whereas ceramide-dependent membrane remodelling contributes to intraluminal-vesicle formation and EV output (Han et al., 2022; Huang et al., 2025; Skotland et al., 2019; Krylova and Feng, 2023). Current CNS-tumour evidence supports these mechanisms as a regulatory framework, but it does not yet establish a complete causal network connecting therapeutic stress, activation of a specific sorting regulator, incorporation of a defined cargo and resistance in recipient cells (Yin et al., 2019; Zhang et al., 2019; Yang et al., 2022b; Ramakrishnan et al., 2020; Han et al., 2026).

5.7. Synergistic effects of EV-mediated resistance with classical resistance mechanisms

In this section, synergy refers to functional cooperation and convergence between EV-mediated communication and established resistance pathways rather than to formally quantified supra-additive effects. EVs can extend resistance beyond the subpopulation in which it initially developed by transferring functional molecules between tumour and stromal cells. Consequently, EV signalling can reinforce DNA repair, drug efflux, survival signalling, stemness, and immune escape without constituting a separate resistance pathway, illustrating how EV-mediated mechanisms intersect with multiple tumour- and microenvironment-associated resistance processes (Fig. 2).

5.7.1. DNA damage repair

EVs can enhance resistance to DNA-damaging therapies by transferring repair-related molecules or altering their expression in recipient cells. Reactive astrocyte-derived EVs deliver MGMT mRNA to glioma cells, where it is translated into functional MGMT protein and increases resistance to TMZ (Yu et al., 2018). Exosomal lncSBF2-AS1 similarly promotes TMZ resistance through the miR-151a-3p–XRCC4 axis, thereby enhancing XRCC4-dependent double-strand-break repair (Zhang et al., 2019). Evidence from irradiated non-CNS cancer models additionally shows that EV proteomes may become enriched in DNA-damage-response proteins, including XRCC5 and XRCC6. These findings identify candidate repair-associated cargo but do not demonstrate that individual proteins are functionally transferred or that the same pattern occurs in CNS tumours (Abramowicz et al., 2019). A more direct CNS-specific mechanism involves radiation-induced EV export of

miR-603. Loss of intracellular miR-603 derepresses IGF1 and IGF1R, promoting a glioblastoma stem-cell state and acquired radioresistance. Simultaneous derepression of MGMT increases resistance to DNA-alkylating agents (Ramakrishnan et al., 2020). EVs may therefore reinforce DNA repair either by delivering functional repair molecules or by removing intracellular suppressors of repair-related pathways.

5.7.2. Drug efflux and pharmacological resistance

Reduced intracellular drug accumulation is a classical mechanism of pharmacological resistance. In glioblastoma, PTRF/Cavin-1 increases EV secretion and promotes TMZ efflux, reducing intracellular TMZ concentration and weakening the resulting DNA-damage response. EV trafficking can therefore limit the initial pharmacological insult before repair and survival pathways become activated (Yang et al., 2022b). In non-CNS multidrug-resistant cancer models, EV-associated P-glycoprotein, encoded by *ABCB1*, has been reported to transfer an efflux phenotype to sensitive cells. This could allow recipient cells to acquire increased drug-export capacity without inducing their own *ABCB1* expression. Equivalent functional transfer, however, remains insufficiently validated in CNS tumours (Xavier et al., 2022; Rigogliuso et al., 2024). Preliminary conference-level evidence from SHH medulloblastoma indicates that EVs from vincristine-tolerant cells increase resistance in sensitive cells and that *ABCB1* inhibition reverses this phenotype. These findings support a role for EVs and *ABCB1* in acquired resistance but do not yet demonstrate direct vesicular transfer and membrane incorporation of functional *ABCB1* (Wade et al., 2023). Thus, EV secretion may cooperate with classical efflux systems by removing drugs from producing cells and potentially transferring drug-export machinery to neighbouring cells. The resulting sublethal drug exposure may provide additional time for DNA repair and adaptive survival signalling (Yang et al., 2022a; Wade et al., 2023).

5.7.3. Survival signaling and apoptosis avoidance

Structurally different EV cargos can converge on a limited number of survival and apoptosis-regulating pathways. Exosomal miR-1238 from TMZ-resistant glioblastoma cells suppresses CAV1 and enhances CAV1/EGFR-associated signalling in sensitive recipient cells (Yin et al., 2019). Exosomal MIF acts through the TIMP3/PI3K/AKT axis, increasing proliferation and reducing apoptosis during TMZ treatment. Both mechanisms connect cargo transfer with activation of established survival programmes rather than with a distinct EV-specific pathway (Wei et al., 2021). Cx43-enriched EVs additionally shift the Bcl-2/Bax/caspase-3 balance towards survival, illustrating how vesicular membrane proteins can reinforce classical apoptosis avoidance (Yang et al., 2021).

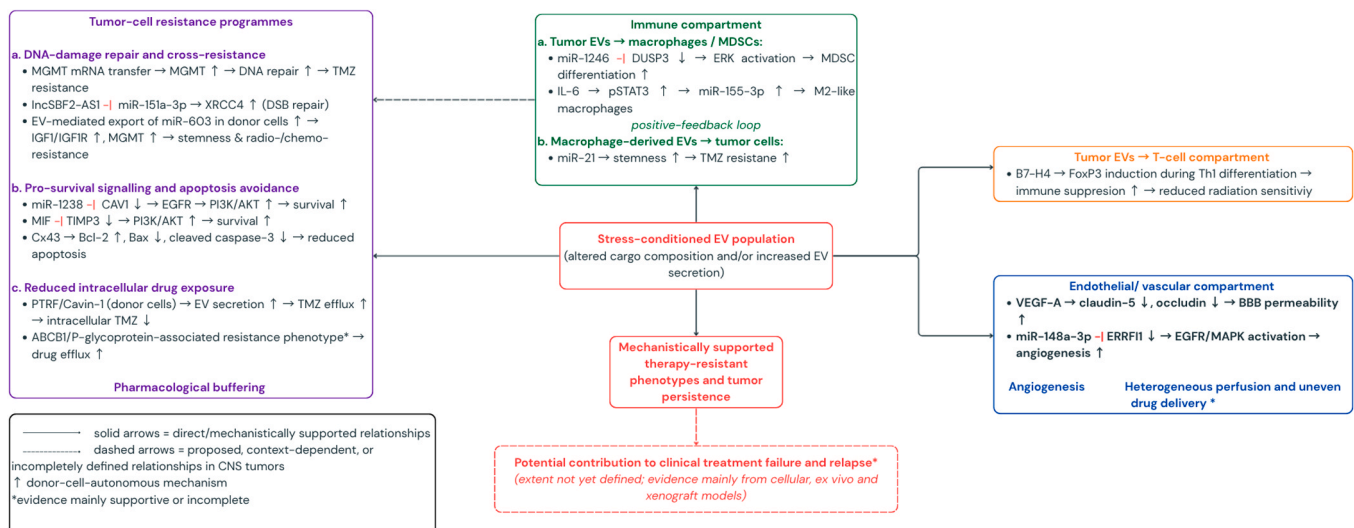


Fig. 2. Extracellular Vesicle-Mediated Mechanisms of Therapy Resistance Across Tumor and Microenvironmental Compartments in Glioma.

Macrophage-derived miR-21-enriched EVs also promote TMZ resistance and stemness-associated features in glioblastoma cells. Consistent with this phenotype, a separate non-vesicular study showed that miR-21 overexpression reduced the Bax/Bcl-2 ratio and caspase-3 activity during TMZ treatment (Shi et al., 2010). These results should be presented as complementary evidence rather than as measurements obtained within the same exosomal model (Chuang et al., 2019). Overall, EV-associated miRNAs, soluble proteins, and membrane proteins converge on EGFR-, PI3K/AKT-, Bcl-2-, and caspase-dependent mechanisms. EV signalling therefore extends the cellular range of classical survival programmes rather than replacing them.

5.7.4. Stemness, immune escape and microenvironmental adaptation

EV-mediated communication also reinforces cellular plasticity and microenvironmental protection. Macrophage-derived miR-21-enriched EVs support stemness-associated programmes in glioblastoma cells (Chuang et al., 2019), whereas radiation-induced export of miR-603 promotes an IGF1/IGF1R-dependent glioblastoma stem-cell state. These mechanisms may preserve tumour-cell populations capable of repopulating the tumour after treatment (Ramakrishnan et al., 2020). Tumour-derived EVs can simultaneously modify immune compartments. Exosomal miR-1246 promotes the differentiation and activation of myeloid-derived suppressor cells (Qiu et al., 2021), while hypoxic glioma-derived EVs induce autophagy-associated M2-like macrophage polarization (Xu et al., 2021). Radiation provides another connection between treatment stress and immune escape: irradiated glioblastoma cells release B7-H4-enriched exosomes that increase FoxP3 expression during Th1-cell differentiation, suppress antitumour immunity, and reduce radiation sensitivity in an experimental mouse model (Tian et al., 2022). EV-mediated adaptation also extends to vascular cells. Hypoxic GBM-derived EVs containing VEGF-A reduce endothelial tight-junction proteins and increase blood–brain barrier permeability (Zhao et al., 2018). Separately, glioma-derived exosomal miR-148a-3p promotes endothelial proliferation and angiogenesis by suppressing ERFF1 and activating EGFR/MAPK signalling. These changes may support protective vascular niches, although their effects on the intratumoural concentration of specific drugs were not directly established in these studies (Wang et al., 2020). Stromal and extracellular-matrix remodelling may additionally impair homogeneous drug delivery, but the direct role of EVs in these processes remains less clearly demonstrated in CNS tumours (Kim et al., 2022; Masuda, 2025; Prakash and Shaked, 2024). MT1-MMP-positive exosomes can mediate focal matrix degradation in a non-CNS cancer model, providing mechanistic plausibility that still requires validation in brain tumours (Palomulli et al., 2025). Overall, EVs connect tumour-cell-intrinsic resistance with protective responses in immune, vascular, and stromal compartments. Rather than constituting an autonomous resistance pathway, extracellular-vesicle signalling acts as an intercellular amplification system that distributes and coordinates classical resistance programmes across spatially separated tumour and stromal compartments.

5.8. Spatial and temporal heterogeneity of resistance-associated EV cargo

CNS tumours contain spatially distinct cellular and microenvironmental compartments, including hypoxic and necrotic regions, perivascular and glioma stem-cell niches, invasive margins, and immune-rich areas. These compartments differ in oxygenation, nutrient availability, pH, inflammatory signalling, and exposure to drugs or radiation. Because EV composition reflects both donor-cell identity and cellular stress, tumour regions with different biological states may produce functionally distinct EV populations. However, this hypothesis should be distinguished from direct evidence obtained by profiling EVs from spatially separated regions of the same tumour.

The strongest evidence concerns hypoxia. Compared with normoxic glioma cells, hypoxic cells release EVs enriched in IL-6 and miR-155-3p that promote autophagy-dependent M2-like macrophage polarization

(Xu et al., 2021). Hypoxic GBM-derived EVs containing VEGF-A also reduce endothelial tight-junction proteins and increase blood–brain barrier permeability (Zhao et al., 2018). In addition, EVs from hypoxic glioma stem-like cells transfer miR-30b-3p and increase TMZ resistance in recipient GBM cells. These findings support stress-dependent EV remodelling but do not directly demonstrate regional differences within an individual tumour (Yin et al., 2021). Therapeutic exposure constitutes another source of temporal and potentially regional heterogeneity. Irradiation changes EV release and molecular composition, although some supporting proteomic and functional studies were conducted in non-CNS cancer or neuroblastoma models (Dong et al., 2024; Abramowicz et al., 2019; Tortolici et al., 2021). In glioblastoma, radiation induces EV-mediated export of miR-603, promoting IGF1/IGF1R-dependent stemness and MGMT-associated cross-resistance, and increases the release of immunosuppressive B7-H4-containing exosomes (Ramakrishnan et al., 2020; Tian et al., 2022). Similarly, TMZ-resistant glioma cells release EVs containing miR-1238, MIF, and Cx43, which differ functionally from vesicles produced by sensitive cells. These findings support treatment-dependent EV remodelling, but do not directly demonstrate differences between more- and less-exposed regions within an individual tumour (Yin et al., 2019; Wei et al., 2021; Yang et al., 2021). Donor-cell identity may further diversify local EV populations. Tumour cells, macrophages, and reactive astrocytes release distinct resistance-associated cargo, including miR-1238, MIF, and Cx43, and MGMT mRNA, respectively (Yin et al., 2019; Chuang et al., 2019; Shi et al., 2010; Yu et al., 2018). Endothelial and immune cells also respond differently to tumour-derived EVs. Such cell-type-specific communication may generate compartment-dependent EV networks within perivascular, immune, or stem-cell-rich niches. Nevertheless, evidence that different donor cells release different EVs should not be treated as equivalent to direct proof of regional EV-cargo heterogeneity (Qiu et al., 2021; Xu et al., 2021; Zhao et al., 2018; Wang et al., 2020).

Although current evidence indicates that donor-cell identity and local stress conditions influence EV composition, direct spatially resolved comparisons of EV cargo obtained from multiple regions of the same human CNS tumour remain limited. Evidence concerning oxygenation and treatment exposure is substantially stronger than evidence for pH- or nutrient-dependent EV remodelling in CNS tumours; the latter should therefore be considered plausible modifiers rather than established determinants.

This limitation has clinical implications. A single tissue biopsy may not capture the complete EV landscape of a heterogeneous tumour. CSF-derived EVs can contain tumour-associated EGFR and EGFRvIII RNA, whereas circulating EV-RNA can be detected in plasma or serum (Figuerola et al., 2017; Batool et al., 2022; Yekula et al., 2023). However, these studies do not establish that CSF and blood contain equivalent proportions of tumour-derived EVs or represent the same tumour compartments. Longitudinal analyses further indicate that circulating EV profiles can change during treatment or disease progression (Ramakrishnan et al., 2020; Batool et al., 2022; Yekula et al., 2023). Future studies should therefore combine multiregional tumour sampling with spatial molecular profiling, single-vesicle analysis, and paired longitudinal CSF and blood collection.

6. Exosome-mediated drug resistance and overview of CNS tumours

The 2021 WHO Classification of Tumours of the Central Nervous System integrates histopathologic and molecular features to define CNS tumour entities and assign WHO grades. Tumours are organized into major families, including adult-type diffuse gliomas, pediatric-type diffuse low- and high-grade gliomas, circumscribed astrocytic gliomas, glioneuronal and neuronal tumours, ependymomas, medulloblastomas and other embryonal tumours, mesenchymal and non-meningothelial tumours, tumours of the sellar region, meningiomas, schwannomas, pineal region tumours, choroid plexus tumours, and primary CNS

Table 2

Common EV-Associated Therapy-Resistance Pathways Across CNS Tumour Types.

Common resistance pathway	Representative EV-mediated mechanisms	CNS tumour and therapy context	Evidence status
DNA-damage repair and radioresistance	Transfer of MGMT mRNA and lncSBF2-AS1; radiation-induced export of miR-603; transfer of repair- and metabolism-associated cargo	Glioblastoma: TMZ and radiotherapy; H3K27-altered diffuse midline glioma: radiotherapy	Direct functional evidence in glioblastoma; recent preclinical evidence in diffuse midline glioma
Pro-survival signalling and apoptosis avoidance	Activation of EGFR-PI3K/AKT/mTOR and TIMP3-PI3K/AKT pathways; modulation of the Bcl-2/Bax/caspase-3 balance; HSP90-associated AKT/ERK signalling	Glioblastoma: mainly TMZ; NF2-associated schwannoma: tumour survival and immune adaptation	Causal resistance evidence in glioblastoma; supportive survival and immune evidence in schwannoma
Drug efflux and reduced intracellular drug exposure	PTRF/Cavin-1-dependent TMZ export; EV-associated ABCB1/P-glycoprotein phenotype	Glioblastoma: TMZ; SHH medulloblastoma: vincristine	Direct evidence for TMZ export in glioblastoma; preliminary evidence in SHH medulloblastoma without conclusive demonstration of functional ABCB1 transfer
Immune escape and reduced treatment sensitivity	MDSC and M2-like macrophage induction; B7-H4-mediated immunosuppression; TAM-derived METTL14-FOXO1 regulation	Glioblastoma: TMZ and radiotherapy; SHH medulloblastoma: response to PD-1 blockade	Preclinical mechanistic evidence in both tumour types; limited clinical validation
Microenvironmental and vascular support of treatment-refractory states	BBB and endothelial remodelling; angiogenic signalling; perivascular and stromal EV communication	Glioblastoma: vascular and immune niches; ependymoma and plexiform neurofibroma: tumour-supportive microenvironment	Direct EV-mediated vascular and immune effects in glioblastoma; supportive evidence in ependymoma and plexiform neurofibroma without direct testing of resistance to a defined therapy

lymphomas and histiocytic tumours (Louis et al., 2021). The common EV-associated resistance pathways shared across these tumour types are summarised in Table 2. The following sections focus on tumour-specific evidence and differences in the strength of mechanistic support.

6.1. Glioblastoma

The glioblastoma tumour microenvironment comprises glioma stem cells, differentiated tumour cells, stromal glia and infiltrating immune cells, whose interactions are partly coordinated by EVs. EV-mediated transfer of oncogenic proteins and regulatory RNAs contributes to tumour heterogeneity, aggressiveness and therapy adaptation (Indira Chandran et al., 2024). As described in Chapter 5, EVs derived from TMZ-resistant glioma cells can transfer Cx43, MIF and resistance-associated RNAs to sensitive cells, thereby enhancing survival, proliferation and TMZ resistance (Yang et al., 2021; Izhar et al., 2025; Wei et al., 2021; Yang et al., 2024; Geng et al., 2022). Glioma stem-cell-derived EVs also promote radioresistance through cargo associated with DNA repair, survival signalling and stress adaptation. Collectively, glioblastoma provides the broadest evidence that EVs can coordinate chemoresistance, radioresistance and microenvironmental adaptation, although most studies remain preclinical (Sun et al., 2022; Ma et al., 2022). The principal EV-associated factors implicated in glioblastoma therapy resistance and their reported mechanisms are summarized in Table 3.

6.2. Medulloblastoma

In SHH-subgroup medulloblastoma, tumour-associated-macrophage-derived exosomes can promote immune-mediated therapeutic resistance through suppression of METTL14, reduced m6A modification and increased FOXO1 expression, thereby limiting CD8⁺ T-cell recruitment and reducing sensitivity to PD-1 blockade (Liu et al., 2025). In addition, EVs from vincristine-tolerant cells can increase vincristine resistance in sensitive cells, with ABCB1 inhibition reversing the acquired phenotype (Wade et al., 2023). Exosomal miR-101-3p, miR-423-5p and other non-coding RNAs may also influence apoptosis, proliferation and stem-like properties, although their direct contribution to treatment resistance remains less established (Xue et al., 2022; Joshi et al., 2019). B7-H3-associated activation of PI3K/AKT represents a further potential mechanism that requires direct validation in medulloblastoma (Purvis et al., 2020). The principal EV-associated factors implicated in medulloblastoma therapy resistance and the corresponding mechanisms are summarized in Table 4.

Table 3

Exosome-Mediated Drug Resistance Factors in Glioblastoma.

Cargo/Factor	Mechanism of Resistance	Type of Resistance
Connexin 43 (Cx43)	Modulates apoptotic regulators in recipient cells, increasing TMZ resistance and survival	Chemoresistance
MIF (Macrophage migration inhibitory factor)	Enhances proliferation, suppresses apoptosis, downregulates TIMP3, activates PI3K/AKT pathway	Chemoresistance
P-glycoprotein	Promotes drug efflux, reducing intracellular temozolomide accumulation	Chemoresistance
Resistance-associated miRNAs (miR-25-3p, miR-221, miR-1238, miR-27a-3p, miR-151a, miR-301a)	Target apoptotic and survival pathways, enhancing proliferation, survival, and chemoresistance	Chemoresistance
MGMT mRNA	Increases DNA repair capacity, conferring temozolomide resistance	Chemoresistance
circWDR62	Sequesters miR-370-3p → upregulates MGMT, modulates PI3K/AKT, promotes proliferation, migration, invasion	Chemoresistance
EGFRvIII	Horizontal transfer of oncogenic receptor, increases tumor aggressiveness and heterogeneity	Chemoresistance
ATM kinase	Enhances DNA damage repair following irradiation, promoting radioresistance	Radioresistance
HIF-1α / angiogenic factors	Activate pro-survival and angiogenic pathways, enhancing radioresistance and adaptation to hypoxia	Radioresistance
Exosomal miRNAs / circRNAs / ncRNAs	Activate PTEN/AKT signaling, modulate apoptosis, and sequester tumor-suppressive miRNAs to reinforce survival and stress adaptation	Radioresistance

6.3. Ependymoma

In ependymoma, multi-omic analyses indicate enhanced EV signalling, particularly from perivascular mesenchymal cells, which may support aggressive and treatment-refractory tumour states. Pharmacological inhibition of sphingomyelinase-dependent EV biogenesis reduced tumour-cell survival and invasion, suggesting that EV

Table 4
Exosome-Mediated Drug Resistance Factors in Medulloblastoma.

Cargo/Factor	Mechanism of Resistance	Type of Resistance
TAM-derived miRNAs	Downregulate METTL14 → reduce m6A RNA modifications → upregulate FOXD1 → suppress CD8 ⁺ T cell recruitment → create immunosuppressive tumor microenvironment	Immunotherapy resistance
ABCB1 (multidrug transporter)	Transferred to sensitive tumor cells → promotes drug efflux → enables survival under chemotherapeutic pressure	Chemoresistance
Exosomal miR-101–3p and miR-423–5p (downregulated)	Loss reduces apoptotic signaling and enhances proliferation, colony formation, and invasion → promotes survival under therapy	Chemoresistance
Subgroup- and stem-cell-specific ncRNAs (lncRNAs, miRNAs)	Maintain stem-like properties, promote metastasis and therapy evasion → contribute to tumor recurrence and treatment resistance	Chemoresistance
B7-H3 (putative exosomal cargo)	Potential upstream activator of PI3K/AKT → induces expression of genes associated with chemoresistance, proliferation, and metabolic adaptation	Chemoresistance

trafficking may represent a therapeutic vulnerability (Pando et al., 2025). EV-mediated effects on angiogenesis, microglial activation, endoplasmic-reticulum stress and the unfolded-protein response may further support tumour adaptation, although direct evidence of resistance to a defined treatment remains limited (Maass et al., 2020).

6.4. Meningioma

In meningioma, several EV-associated proteins, including MUC1, SIGLEC11, E-cadherin, KIT and TACSTD2, are elevated before surgery and decrease following tumour resection, supporting their tumour-

Table 5
Exosome-Mediated Drug Resistance Factors in Meningioma.

Cargo/Factor	Mechanism of Resistance	Type of Resistance
MUC1 (EV-enriched protein)	EV-associated MUC1 may activate PI3K/AKT and MAPK signaling, enhance anti-apoptotic pathways, and promote metabolic adaptation; elevated preoperatively and reduced after tumor resection, supporting tumor-derived origin	Chemoresistance (putative)
↓ Exosomal miR-497	GATA4 overexpression suppresses miR-497 → derepression of Cyclin D1 → enhanced G1/S transition, proliferation, and survival under therapeutic stress	Chemoresistance
↓ Exosomal miR-195	Loss of tumor-suppressive regulation of cell cycle-associated targets; reduced exosomal levels correlate with higher tumor grade	Chemoresistance (correlative)
Caveolin-1 (Cav-1)	Regulates caveolae-mediated endocytosis, vesicular trafficking, and membrane compartmentalization of oncogenic signaling complexes; may influence EV uptake and amplification of survival pathways	Chemoresistance / Potential radioresistance
Increased circulating EV burden	Elevated systemic EV levels reflect aggressive tumor biology and enrichment of oncogenic proteins and regulatory RNAs; postoperative decline suggests dynamic tumor dependency	Therapy refractoriness (biomarker of aggressive phenotype)

derived origin (Zhou et al., 2024). High-grade meningiomas also show alterations in exosomal miR-497 and miR-195 that may be associated with proliferative and treatment-refractory phenotypes (Rana et al., 2021). EV-associated Cav-1 may influence vesicle trafficking, uptake and BBB-related delivery, whereas circulating EV abundance correlates with tumour grade, oedema and postoperative tumour burden. These findings are primarily biomarker-oriented and do not yet establish direct EV-mediated chemo- or radioresistance (Pando et al., 2025; Ricklefs et al., 2022). The available EV-associated factors and their potential relevance to therapeutic resistance in meningioma are summarized in Table 5.

6.5. Pituitary adenomas

Aggressive pituitary adenomas can exhibit resistance to dopamine agonists, chemotherapy and radiotherapy. Resistance-associated miRNAs, including miR-145–5p and miR-93–5p, regulate pathways involved in proliferation, survival and stromal remodelling. Their potential packaging into exosomes suggests a mechanism for intercellular dissemination of treatment-refractory phenotypes, although direct functional evidence remains limited (Gareev et al., 2021).

6.6. Schwannoma

EVs contribute to schwannoma biology through the transfer of regulatory miRNAs and proteins. In vestibular schwannoma, EV-associated miR-431–5p may affect cochlear-cell stress responses, whereas Cav-1 may regulate vesicle uptake and trafficking (Pando et al., 2025). In NF2-associated schwannoma, exosomal HSP90 supports AKT/ERK-dependent survival signalling and MDSC-associated immune suppression. These effects may contribute to treatment refractoriness, although resistance to a defined therapy has not yet been demonstrated (Wang et al., 2025).

6.7. Plexiform neurofibroma

In plexiform neurofibroma, fibroblast-derived small EVs promote spheroid growth and invasive outgrowth. Depletion of sEVs from fibroblast-conditioned medium reduces these effects, supporting a functional role for stromal vesicle signalling in maintaining a tumour-supportive microenvironment. However, direct EV-mediated resistance to a defined treatment has not yet been shown (Ji et al., 2024).

6.8. Diffuse midline glioma, H3K27-altered

H3K27-altered diffuse midline gliomas are intrinsically resistant to radiotherapy. Recent evidence indicates that sEVs released by radio-resistant tumour subclones are taken up by radiosensitive cells and increase their survival following irradiation. Their cargo includes proteins, miRNAs and metabolites associated with DNA repair and energy metabolism, promoting repair and metabolic adaptation in recipient cells. These findings support a lineage- and therapy-specific EV resistance programme, although clinical validation in pediatric cohorts remains lacking (Oza et al., 2025).

6.9. Primary CNS lymphoma (PCNSL)

In primary CNS lymphoma, therapeutic failure is frequently related to restricted BBB transport and exposure-limiting toxicity rather than established endogenous EV-mediated resistance. Engineered anti-CD19-decorated exosomes loaded with methotrexate promoted BBB transcytosis, prolonged CSF drug exposure and improved tumour control in intracranial models compared with free methotrexate. These findings support EVs as a targeted delivery strategy rather than as confirmed mediators of intrinsic methotrexate resistance (Zhao et al., 2025).

6.10. Brain metastases (BM)

In brain metastases, EVs contribute to communication between metastatic tumour cells and the brain microenvironment. Regulated vesicle uptake by endothelial and other recipient cells supports brain tropism, niche remodelling and tumour adaptation. Current evidence therefore positions EVs primarily as mediators of brain colonisation, candidate biomarkers and potential drug-delivery platforms, whereas their direct role in transferring resistance to defined therapies remains less established (Oliveira et al., 2021).

7. Therapeutic and diagnostic translation of EVs in CNS tumours

In glioblastoma and other CNS tumours, extracellular vesicles (including exosome-enriched small EVs) are actively being evaluated both as drug-delivery vehicles and as substrates for minimally invasive “liquid biopsy” strategies (Cela et al., 2024; Hao et al., 2024). Because the label “exosome” is frequently used imprecisely across studies, translation toward clinical use depends on rigorous EV isolation, characterization, and reporting standards (C et al., 2018).

Preclinical work supports feasibility of EV-based CNS delivery, including systemic administration of engineered exosomes for brain-targeted siRNA delivery and orthotopic glioblastoma targeting with therapeutic, engineered MSC exosomes (Alvarez-Erviti et al., 2011; Haltom et al., 2022).

7.1. Targeting EVs to overcome resistance

Experimental evidence indicates that EVs can disseminate therapy-resistance traits in glioblastoma by transferring functional RNA/protein cargo from resistant to sensitive tumour cells (Yin et al., 2019; Wei et al., 2021).

Representative examples include transfer of miR-1238 from TMZ-resistant cells and hypoxia-associated delivery of miR-30b-3p from glioma stem-like cells, both of which increased TMZ resistance in recipient cells (Yin et al., 2019, 2021). These findings support strategies that interfere with EV uptake. Heparin was shown to interact with brain-tumour-cell-derived EVs and reduce their transfer to recipient cells at concentrations considered clinically achievable in vitro. However, this observation represents proof of principle rather than evidence of tumour-selective EV inhibition or clinical antitumour efficacy (Atai et al., 2013). Strategies aimed at reducing EV release have also been explored. Inhibition of neutral sphingomyelinase-dependent EV biogenesis with GW4869 suppressed malignant behaviour and restored TMZ sensitivity in a GBM model in association with glucose-metabolic remodeling. Nevertheless, GW4869 affects ceramide-dependent lipid pathways and should be considered an experimental pathway inhibitor rather than an EV-specific therapeutic agent (Han et al., 2026). Future studies should assess target specificity, CNS pharmacokinetics, off-target effects, and the consequences of repeated EV inhibition. Experimental designs should also include EV-depleted conditioned-medium controls, cargo-specific perturbation, dose-response analyses, and rescue or add-back experiments to distinguish genuine EV-mediated effects from soluble mediators or non-specific pharmacological activity. Current EV-targeting strategies therefore remain preclinical and require substantially stronger efficacy and safety validation before clinical implementation (Cela et al., 2024).

7.2. EVs as biomarkers

CSF-derived EVs provide a high-proximity biospecimen for brain tumours, and a multi-institutional study demonstrated detection of tumour-associated EGFR amplification and EGFRvIII mutation using RNA extracted from CSF EVs of GBM patients (Figuerola et al., 2017). In peripheral blood, a clinically oriented study reported that EGFRvIII transcripts could be detected from paired serum-exosome samples,

supporting the feasibility of non-invasive molecular stratification in high-grade glioma (Manda et al., 2018). Analytical sensitivity has been further improved with circulating EV-RNA assays using droplet digital PCR for EGFRvIII detection in glioma patients (Batool et al., 2022).

EV-based liquid biopsy can also function as a longitudinal pharmacodynamic readout, as shown by serial profiling of serum-derived EV RNA in EGFR-amplified recurrent GBM patients treated with the EGFR TKI dacomitinib (Yekula et al., 2023). In an intraventricular CAR T-cell trial targeting EGFRvIII/EGFR, serial CSF extracellular-vesicle RNA measurements showed EGFRvIII and EGFR copy numbers decreasing over time (and becoming undetectable in post-treatment CSF samples in participants), illustrating response monitoring via EV-RNA (Choi et al., 2024). Beyond blood and CSF, urinary EVs are being assessed as a non-invasive matrix for glioblastoma-associated biomarker panels using in-depth proteomic profiling (Hallal et al., 2024). EV protein cargo may also carry clinically relevant signals, for example, EVs carrying Tenascin-C were reported as clinical indicators associated with glioblastoma tumour activity in an ACS Nano study (Salviano-Silva et al., 2025). Across biofluids, robust clinical translation depends on harmonised pre-analytics and EV characterization standards, as formalised in the ISEV MISEV2018 position statement (C et al., 2018). Overall, EV-based biomarkers offer promise for minimally invasive molecular profiling and longitudinal monitoring in CNS tumours, but their clinical use remains limited by biological variability, dilution of tumour-derived signals, and insufficient analytical standardisation and prospective validation. Recent clinical-cohort studies nevertheless provide preliminary evidence supporting their feasibility for treatment stratification and monitoring. A secondary analysis of a multicentre dacomitinib trial longitudinally profiled serum EV RNA in 14 patients with EGFR-amplified recurrent glioblastoma, including seven responders and seven nonresponders, and identified baseline ZNF35 and LAMTOR2 and post-treatment DNMT3A as candidate response-associated EV RNAs (Yekula et al., 2023). In the first-in-human intraventricular CARv3-TEAM-E study (n = 3), serial CSF EV measurements showed declining EGFRvIII and EGFR copy numbers after treatment (Choi et al., 2024). Two additional cohorts broadened the range of biofluids and analytical approaches: proteomic analysis of 50 urine specimens from 24 patients identified EV panels associated with tumour burden and recurrence (Hallal et al., 2024), whereas plasma immunophenotyping in 37 newly diagnosed and 11 recurrent glioblastoma cases demonstrated marked enrichment of TNC + /CD9 + EVs. Collectively, these studies support the clinical feasibility of EV-based treatment stratification and longitudinal monitoring, although their exploratory sample sizes and biomarker-oriented designs do not establish causal transfer of drug resistance in patients (Salviano-Silva et al., 2025). The interpretation and reproducibility of such findings depend on consistent methodological standards. MISEV2018, which updated the MISEV2014 framework, established principles directly relevant to resistance research, including the use of operational EV terminology when endosomal origin has not been demonstrated, transparent reporting of sample collection and separation procedures, quantitative particle and protein measurements, assessment of multiple positive EV-associated markers together with non-EV contaminants, and the application of orthogonal structural and functional controls (C et al., 2018). These requirements are not merely technical, because co-isolated lipoproteins, ribonucleoprotein complexes or incompletely characterised EV mixtures may otherwise lead to erroneous attribution of biomarker signals or resistance-associated phenotypes specifically to exosomes and impede reproducibility across clinical cohorts.

7.3. Engineered EVs for overcoming resistance in CNS tumours

Engineered EVs provide a complementary approach to inhibiting endogenous vesicle-mediated communication. Their membranes can be modified with targeting ligands, whereas their lumen can be loaded with therapeutic nucleic acids or small-molecule drugs. The principal

objective is not simply to cross the blood–brain barrier, but to improve cargo stability, CNS exposure and uptake by the intended tumour-cell population (Hao et al., 2024). An early proof-of-concept study used dendritic-cell-derived exosomes expressing Lamp2b fused to a rabies-virus-glycoprotein-derived peptide. Following intravenous administration in mice, these vesicles delivered siRNA to neurons, microglia and oligodendrocytes and produced target-gene knockdown in the brain. However, this study was conducted outside a tumour model and therefore demonstrated brain-directed delivery rather than glioma-specific targeting (Alvarez-Erviti et al., 2011). More direct evidence is available in glioblastoma. Human bone-marrow-MSC-derived exosomes engineered to carry MYC-targeting siRNA localised to orthotopic GBM tumours after systemic administration. Treatment reduced MYC expression, proliferation, angiogenesis and tumour growth, prolonged survival and induced a transcriptional shift from a mesenchymal towards a proneural state. These findings support the feasibility of using engineered EVs to target an oncogenic pathway that remains difficult to inhibit pharmacologically. Nevertheless, the evidence was obtained in preclinical models and does not establish generalisable delivery across the molecular and spatial heterogeneity of human GBM (Haltom et al., 2022). A distinct strategy has been investigated in CNS lymphoma. Human adipose-MSC-derived exosomes were engineered to display an anti-CD19 targeting component and loaded with methotrexate. In experimental BBB and intracranial lymphoma models, anti-CD19-Exo-MTX increased CNS drug exposure, enhanced uptake by CD19-positive lymphoma cells, inhibited tumour growth and prolonged survival compared with free methotrexate. This platform therefore addressed both inadequate CNS exposure and cellular targeting, although its efficacy and safety remain untested in patients (Zhao et al., 2025). The current primary evidence in the bibliography consequently supports brain-directed siRNA delivery, MYC-targeting siRNA in GBM and methotrexate delivery in CNS lymphoma (Zhao et al., 2025; Alvarez-Erviti et al., 2011; Haltom et al., 2022). Delivery of therapeutic miRNAs, proteins and immunomodulatory molecules represents a broader platform opportunity, but the corresponding CNS-tumour evidence is more heterogeneous and should not be presented as equally established (Hao et al., 2024). Compared with conventional synthetic nanoparticles, engineered EVs are proposed to provide a biologically derived membrane, protection of labile cargo and opportunities for surface-guided targeting (Hao et al., 2024). However, these potential advantages are platform-dependent and have rarely been demonstrated in controlled head-to-head comparisons using equivalent cargo, dose and administration routes. Unresolved issues include biodistribution, uptake by non-tumour cells, cargo-loading efficiency, ligand stability and the proportion of administered EVs that reaches the therapeutically relevant tumour compartment (Zhao et al., 2025; Hao et al., 2024; Alvarez-Erviti et al., 2011; Haltom et al., 2022).

7.4. Barriers to clinical translation of EV-based approaches

7.4.1. Biological barriers

EV composition varies between patients, tumour subtypes, anatomical regions, and treatment stages. Hypoxia, irradiation and chemotherapy may alter vesicle release and cargo, meaning that a target identified before treatment may not remain dominant during recurrence (Ramakrishnan et al., 2020; Yin et al., 2021; Indira Chandran et al., 2024). The functionally relevant EV population may originate from malignant cells, macrophages, astrocytes, endothelial cells, or other stromal compartments. Moreover, EV effects are not uniformly tumour-promoting: astrocyte-derived sEVs have been shown experimentally to suppress glioma growth and invasion through transfer of miR-124 (Serpe et al., 2022). Global inhibition could therefore disrupt physiological or tumour-restraining communication together with resistance-associated signalling. Accordingly, exosome-mediated resistance is a temporally evolving phenotype, not a fixed cargo inventory. Ionising radiation, hypoxia and temozolomide can alter EV release and

remodel protein, miRNA and metabolic cargo, so pre-treatment vesicles may differ from those driving persistence or relapse (Abramowicz et al., 2019; Ramakrishnan et al., 2020; Li et al., 2022; Yin et al., 2021; Oza et al., 2025). Longitudinal sampling at baseline, on treatment, response and recurrence, coupled to single-vesicle and functional assays, could distinguish transient stress responses from stable resistance programmes; serial EV-RNA monitoring is already feasible in recurrent glioblastoma (Yekula et al., 2023). Candidate biomarkers and therapeutic EV targets should therefore be validated at the treatment stage in which they are intended to guide care.

7.4.2. Analytical barriers

Most separation methods enrich heterogeneous EV populations and do not specifically isolate endosome-derived exosomes. Preparations from plasma, serum, or conditioned medium may contain lipoproteins, protein aggregates, and non-vesicular RNA–protein complexes. Differences in normalisation by particle number, protein concentration, sample volume or donor-cell number further restrict comparisons between studies. The term “EV” should therefore be preferred unless vesicle biogenesis has been demonstrated, and sample collection, separation, characterisation, purity assessment and normalisation should be reported transparently (Lai et al., 2022; C et al., 2018). EV isolation and characterisation have progressively evolved from conventional bulk approaches, particularly differential ultracentrifugation, towards more selective methods such as size-exclusion chromatography and immunoaffinity isolation, and more recently to microfluidic and single-vesicle technologies. These advances may improve the resolution of heterogeneous EV populations and facilitate the identification of resistance-associated EV subpopulations and cargo-specific changes that may be obscured in bulk analyses (Lai et al., 2022).

7.4.3. Pharmacological barriers

Therapeutic EVs must reach the relevant CNS and tumour compartments while avoiding rapid clearance and non-specific uptake. Surface modification may improve targeting but may also alter circulation time, stability, immune recognition and interactions with non-tumour cells. Additional unresolved variables include the relationship between particle dose and active cargo dose, cargo leakage, repeated administration, immunogenicity, and long-term toxicity (Hao et al., 2024). The markedly different targeting strategies used in the brain-directed siRNA, GBM and CNS-lymphoma models demonstrate that biodistribution and cellular specificity must be established separately for each product rather than inferred from the general properties of EVs (Zhao et al., 2025; Alvarez-Erviti et al., 2011; Haltom et al., 2022).

7.4.4. Manufacturing and quality-control barriers

Clinical translation requires scalable production with defined source cells, culture conditions, harvest intervals, separation methods, and cargo-loading procedures. Batch-to-batch variability may affect particle concentration, molecular composition, potency, and safety. Storage conditions, freeze–thaw stability, sterility, cargo retention and validated potency assays must therefore form part of product-quality assessment (Lai et al., 2022; Hao et al., 2024; C et al., 2018). Current evidence does not support a universally applicable manufacturing workflow, and each engineered EV product will require a clearly defined identity, reproducible release criteria and demonstration that biological activity is retained during storage and administration. Collectively, clinical translation will require not only demonstration of EV-mediated cargo delivery, but also identification of the relevant EV population, cargo-specific causality, reproducible manufacturing and product-specific evidence of biodistribution, efficacy and safety.

7.5. Controversies regarding the clinical relevance of exosomal resistance

Although experimental studies demonstrate that EVs can transfer resistance-associated signals, the quantitative relevance of this

mechanism under physiological conditions remains uncertain. In vitro functional assays frequently expose recipient cells to isolated and concentrated EV preparations. For example, TMZ-sensitive glioblastoma cells were treated with exosomes at 30 µg/mL for 48 h in the study of EV-associated miR-1238 (Yin et al., 2019). Such experiments demonstrate that EV transfer can modify treatment response under controlled conditions, but they do not establish that recipient cells experience an equivalent particle concentration, exposure duration or active-cargo dose within human CNS tumours. Comparisons between studies are additionally complicated by differences in EV dose normalisation based on particle number, total protein, sample volume or donor-cell number (Lai et al., 2022; C et al., 2018). Dose-response assessment and transparent reporting of EV characterisation and normalisation are therefore necessary for evaluating the physiological relevance of functional findings (Lai et al., 2022; C et al., 2018). A second controversy concerns the distinction between EV-associated effects and cargo-specific causality. Global suppression of EV production or release can demonstrate that vesicle-associated communication contributes to a phenotype, but it does not by itself identify which EV population or molecular cargo is necessary for that effect. Inhibition with GW4869 was associated with glucose-metabolic remodelling, suppression of malignant behaviour and restoration of TMZ sensitivity in an experimental glioblastoma model (Han et al., 2026). However, GW4869 acts through neutral-sphingomyelinase- and ceramide-dependent pathways and should not be regarded as a selective inhibitor of all tumour-derived EVs (Skotland et al., 2019; Krylova and Feng, 2023; Han et al., 2026). Similarly, PTRF/Cavin-1-dependent secretion promotes TMZ efflux through EVs, but manipulation of this overall secretory process does not independently establish which vesicular component mediates resistance (Yang et al., 2022b). The attribution of biological activity specifically to EVs requires appropriate fractionation and functional controls. Studies should quantitatively compare the activity of complete conditioned medium or biofluid, the same material after EV depletion, isolated EVs, and corresponding non-EV fractions. Negative controls and dose-response analyses are also required to exclude soluble proteins, non-vesicular RNA-protein complexes, co-isolated molecules, and other experimental contaminants as alternative explanations. These controls determine whether a phenotype is EV-associated, but cargo-specific causality additionally requires perturbation of a defined RNA or protein and confirmation that the corresponding treatment response changes without a non-specific alteration in total EV production (C et al., 2018). The available evidence varies substantially in mechanistic strength. Studies involving defined cargo manipulation provide stronger causal support than observations based exclusively on EV enrichment or global inhibition of vesicle release. Exosomal miR-1238 depletion altered TMZ resistance and the associated CAV1/EGFR pathway (Yin et al., 2019), modulation of IncSBF2-AS1 affected the miR-151-a-3p-XRCC4 DNA-repair axis and TMZ response (Zhang et al., 2019), and restoration of miR-603 counteracted radiation-associated resistance mechanisms (Ramakrishnan et al., 2020). Nevertheless, these mechanistic findings were obtained predominantly in cell-based, ex vivo or xenograft models, although some studies also included patient specimens or clinical associations (Yin et al., 2019; Zhang et al., 2019; Ramakrishnan et al., 2020). They therefore support the biological plausibility of EV-mediated resistance but do not yet establish its quantitative contribution to treatment failure in patients. Clinical relevance should consequently be distinguished from experimental causality and from biomarker associations until these mechanisms are prospectively validated in patient cohorts (Cela et al., 2024).

8. Crosstalk between CNS tumour and immune/stromal cells via exosomes

In glioblastoma and other CNS tumours, tumour-derived extracellular vesicles are increasingly viewed as a biologically meaningful route for signalling between malignant cells and the immune/stromal

compartments of the brain tumour microenvironment (Yekula et al., 2020). Intravital two-photon microscopy in orthotopic mouse glioma models has directly visualized vesicle release from glioma cells and subsequent uptake by resident microglia and infiltrating monocytes/macrophages within the brain (Yekula et al., 2020; Van Der Vos et al., 2016). Notably, microglial uptake of glioblastoma EVs in this setting was accompanied by increased microglial proliferation and a shift in cytokine output toward immune suppression, alongside transfer of vesicle-associated miRNAs with corresponding changes in recipient-cell transcripts (Van Der Vos et al., 2016). Beyond myeloid cells, classic work showed that glioblastoma microvesicles/exosome-enriched fractions can be taken up by brain microvascular endothelial cells and stimulate endothelial tubule formation, supporting a pro-angiogenic remodelling of the perivascular niche (Skog et al., 2008). EV communication also extends to astrocytic stromal elements: glioblastoma EV-containing conditioned media promoted proliferation/self-renewal and colony formation of *pre-transformed* astrocytes and induced gene-expression and metabolic shifts consistent with horizontal transfer of full-length mRNAs linked to oxidative phosphorylation and glycolysis (Zeng et al., 2020). On the immune axis, glioblastoma-derived EVs have been shown to skew peripheral blood monocytes toward alternatively activated/M2-type macrophage differentiation, with altered cytokine secretion, and to induce tumour-supportive features in primary human microglia (de Vrij et al., 2015). Mechanistic studies further indicate that defined EV cargos can drive this reprogramming, for example, hypoxic glioma-derived exosomes enriched in miR-1246 markedly induced M2 macrophage polarization and promoted glioma proliferation, migration, and invasion in vitro and in vivo (Qian et al., 2020). In parallel, glioblastoma stem cell-derived exosomes show preferential uptake by monocytes, traverse the monocyte cytoplasm, reorganize the actin cytoskeleton, and induce an M2-like programme with PD-L1 upregulation, linked to STAT3-pathway components present within the exosomal cargo (Gabrusiewicz et al., 2018). Checkpoint signalling can itself be vesicle-borne: glioblastoma-derived EVs expressing surface PD-L1 were reported to block T-cell activation and proliferation after TCR stimulation, and this blockade was significantly reversed by PD-1 receptor blockade only when PD-L1 was present on EVs (Ricklefs et al., 2018). Other data highlight that EV-mediated immunosuppression may also be indirect, glioblastoma EVs can induce immunosuppressive monocyte populations that then inhibit T-cell proliferation, rather than acting primarily through direct T-cell inhibition in every experimental context (Hines et al., 2020). Importantly, this “conversation” is bidirectional: macrophages reprogrammed by glioblastoma exosomes can release their own exosomes carrying pro-tumour factors that enhance glioblastoma cell migration and proliferation, amplifying tumour-supportive dynamics within the microenvironment (Azambuja et al., 2020). At the same time, astrocyte-derived small EVs can also carry anti-tumour activity in experimental models, transfer of astrocyte EV cargo was reported to reduce glioma cell migration and invasion, underscoring that EV-mediated crosstalk is not intrinsically one-directional or uniformly tumour-promoting (Serpe et al., 2022).

9. Conclusion and future perspectives

Exosome-enriched small extracellular vesicles provide CNS tumours with a versatile communication layer that complements genetic evolution by enabling rapid, non-genomic adaptation under therapeutic pressure. Their composition, defined by regulated biogenesis and cargo sorting, creates a mobile package of signalling proteins, membrane receptors, lipids and coding/non-coding RNAs that can reprogram recipient tumour cells and reshape surrounding immune, vascular and stromal compartments. Across CNS tumour contexts, the most reproducible resistance logic is not a single pathway, but the *coordination* of multiple protective programs distributed through vesicle exchange. First, exosomes propagate resistance traits horizontally. Resistant

tumour subclones and therapy-conditioned stromal cells can transmit miRNA/lncRNA circuits and DNA-repair capacity to otherwise sensitive cells, functionally spreading chemoresistance and supporting survival after genotoxic stress. Second, exosomal cargo converges on canonical survival networks, particularly PI3K/AKT and MAPK/ERK, reducing apoptosis and sustaining proliferative competence during treatment. Third, exosomes remodel the tumour microenvironment into a therapy-permissive niche by promoting myeloid immunosuppression, angiogenic plasticity, and extracellular-matrix remodeling. These changes are mechanistically important because they simultaneously support tumour-cell fitness and create physical/biochemical barriers that impair drug delivery, a challenge that is amplified in the CNS by blood-brain barrier constraints. Fourth, a complementary, pharmacology-facing mechanism emerges in which vesicle trafficking lowers effective intracellular drug exposure by exporting chemotherapeutics and/or disseminating drug-export machinery, thereby maintaining sublethal drug concentrations in neighboring clones. Future development of the field is likely to follow three interconnected scenarios, all of which should be considered within a dynamic rather than static model of resistance. Therapeutic pressure can remodel EV cargo composition and release over time while simultaneously selecting resistant subclones with distinct vesicle-producing phenotypes. Longitudinal analyses are therefore needed to distinguish active stress-induced cargo reprogramming from non-selective increases in EV secretion and clonal selection (Ramakrishnan et al., 2020; Yin et al., 2021; Indira Chandran et al., 2024). The first scenario involves spatially resolved EV profiling. Combining single-vesicle analysis with spatial transcriptomics and proteomics could move the field beyond bulk measurements and map resistance-associated vesicle programmes across hypoxic, invasive, perivascular, immune-rich and post-treatment tumour niches. Integration with multiregional tumour sampling and serial CSF and blood collection may help determine which subclones produce specific EV populations, how these signals are transmitted between cellular compartments and whether they represent causal resistance mechanisms or biomarkers of local tissue composition (Lai et al., 2022; Cela et al., 2024; Indira Chandran et al., 2024).

The second scenario concerns the staged clinical translation of engineered EVs designed to overcome BBB-related delivery limitations. Development should include tumour-specific ligand and therapeutic-cargo selection, demonstration of BBB penetration and target-cell uptake in relevant patient-derived and orthotopic models, quantitative biodistribution, GMP-compatible manufacturing, validated potency and release assays, repeat-dose toxicology and subsequent biomarker-enriched early-phase trials (Lai et al., 2022; Zhao et al., 2025; Hao et al., 2024; C et al., 2018; Alvarez-Erviti et al., 2011; Haltom et al., 2022). Comparative clinical evaluation should follow only after reproducible delivery to the intended CNS compartment, pharmacodynamic target engagement and a defined dose-response relationship have been demonstrated. The third scenario involves standardised EV characterisation and reporting as an enabler of multicentre and, ultimately, registration studies. MISEV-aligned terminology, prespecified pre-analytical procedures, transparent EV identity and purity metrics, consistent dose normalisation, assay-performance criteria, manufacturing release specifications and inter-laboratory reproducibility would improve the comparability and auditability of clinical datasets. Such standards may reduce methodological variability and support interpretable trial endpoints, but they cannot replace product-specific requirements for manufacturing quality, biodistribution, safety, efficacy and prospective clinical validation (Lai et al., 2022; C et al., 2018). Together, these three development pathways may determine whether EV-related findings progress from mechanistic observations and exploratory biomarkers to reproducible diagnostic and therapeutic applications capable of improving responses to chemotherapy, targeted therapy, immunotherapy and radiotherapy in CNS tumours.

Critical view

This review provides an integrated critical synthesis of extracellular vesicle (EV)-mediated therapy resistance across central nervous system (CNS) tumours. Whereas much of the existing literature has focused on EV biology, individual resistance-associated cargos, or the diagnostic and biomarker potential of EVs, the present review examines EV-mediated communication specifically within the mechanistic framework of therapeutic resistance. Particular emphasis is placed on how stress-responsive EV biogenesis and cargo selection contribute to the transfer of resistance determinants and converge with established resistance mechanisms, including DNA damage repair, drug efflux, survival signalling, apoptosis avoidance, stemness, immune escape, and tumour microenvironmental adaptation. This mechanistic integration distinguishes the present review from approaches that primarily catalogue EV-associated molecules or consider EVs predominantly as biomarkers.

The scope of this review encompasses the molecular composition and biogenesis of EVs, their role in intercellular communication, the mechanisms underlying EV-mediated chemo- and radioresistance, and their interactions with classical cellular resistance pathways. Evidence is considered across major primary and secondary CNS tumours, including glioblastoma, medulloblastoma, ependymoma, meningioma, pituitary adenomas, schwannoma, plexiform neurofibroma, diffuse midline glioma, primary CNS lymphoma, and brain metastases. The depth of coverage extends from molecular regulators of EV biogenesis and stress-responsive cargo selection to functional resistance transfer, tumour-microenvironment interactions, spatial and temporal heterogeneity, and therapeutic and diagnostic translation. Importantly, mechanistic and functional evidence is distinguished from preclinical associations and emerging clinical observations, allowing the strength of evidence to be considered separately for individual tumour entities and resistance mechanisms.

From a critical perspective, the available evidence does not support an equivalent role for EV-mediated resistance across all CNS tumour types. Glioblastoma provides the strongest functional evidence, whereas in several other CNS tumours the literature remains predominantly descriptive, biomarker-oriented, or based on indirect associations. A major conceptual limitation is the frequent gap between association and causality: altered EV abundance or cargo following therapeutic exposure does not necessarily demonstrate that EVs are required or sufficient for the resistant phenotype. Similarly, pharmacological inhibition of EV biogenesis, EV depletion, inhibition of vesicle release, and manipulation of individual cargos address different biological questions and should not be considered interchangeable evidence of EV-mediated resistance. Experimental EV concentrations, simplified in vitro systems, and insufficient consideration of spatial and temporal heterogeneity further limit translation to the complex CNS tumour microenvironment. In our view, the central challenge for the field is therefore to move from identifying resistance-associated EV signatures towards establishing which EV populations and cargos are causal drivers of treatment failure.

By distinguishing well-supported mechanisms from emerging associations and identifying tumour-specific gaps in evidence, this review provides a structured framework for interpreting a rapidly expanding but heterogeneous literature. This perspective may help prioritize future studies towards cargo-specific functional validation, physiologically relevant EV exposure, spatially and temporally resolved analyses, and standardized EV isolation, characterization, and reporting. Ultimately, progress towards clinical translation will depend on demonstrating that specific EV-dependent interactions constitute therapeutically actionable vulnerabilities rather than secondary markers of tumour adaptation or consequences of parallel non-vesicular resistance mechanisms.

Institutional review board statement

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Author contributions

Conceptualization, all authors; methodology, M.M and K.M.; validation, all authors; investigation, M.M and K.M.; data curation, M.M and K.M writing—original draft preparation, M.M and K.M.; writing—review and editing, all authors; visualization, M.M and K.M supervision, N.R.; funding acquisition, N.R. All authors have read and agreed to the published version of the manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly to improve language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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