Seminars in Cancer Biology 101 (2024) 25–43

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Extracellular vesicles in glioblastoma: Biomarkers and therapeutic tools

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ARTICLE INFO

Keywords:
Glioblastoma
Extracellular vesicles
Liquid biopsy
Targeted therapy

ABSTRACT

Glioblastoma (GBM) is the most aggressive tumor among the gliomas and intracranial tumors and to date prognosis for GBM patients remains poor, with a median survival typically measured in months to a few years depending on various factors. Although standardized therapies are routinely employed, it is clear that these strategies are unable to cope with heterogeneity and invasiveness of GBM. Furthermore, diagnosis and monitoring of responses to therapies are directly dependent on tissue biopsies or magnetic resonance imaging (MRI) techniques. From this point of view, liquid biopsies are arising as key sources of a variety of biomarkers with the advantage of being easily accessible and monitorable. In this context, extracellular vesicles (EVs), physiologically shed into body fluids by virtually all cells, are gaining increasing interest both as natural carriers of biomarkers and as specific signatures even for GBM. What makes these vesicles particularly attractive is they are also emerging as therapeutical vehicles to treat GBM given their native ability to cross the blood-brain barrier (BBB). Here, we reviewed recent advances on the use of EVs as biomarker for liquid biopsy and nanocarriers for targeted delivery of anticancer drugs in glioblastoma.

1. Introduction

Accounting for 12–15 % of all intracranial tumors, GBM is the most lethal and incurable glioma (WHO central nervous system (CNS) grade IV glioma [1]) with an incidence of about 3 per 100 000 adults per year [2] and a dire prognosis (14–15 months of estimated survival [3]). GBM is characterized by inter-patient and intra-tumoral heterogeneity as a result of genetic and epigenetic alterations occurring at significant loci (i.e., TP53, PTEN, EGFR, IDH1, PIK3) in the cancer cells as well as the complex cellular composition of the tumor microenvironment (TME) [4,5]. Mutational and transcriptome profile analysis led to GBM classification into four subgroups (namely classic, neural, proneural, and mesenchymal) in an attempt to stratify patients for tailored therapy [6,7]; however, these subgroups can intra-convert or co-exist during tumor progression [8–10]. As highlighted in recent works, GBM tumor progression, resistance and recurrence might all be facilitated by a pool of GBM stem-like cells (GSCs) with self-renewing and tumor-initiating properties that represent an active portion of the GBM TME [11,12]. From a therapeutical perspective, GBM management is still challenging: due to the late onset of severe symptoms, which delays diagnosis [13] and patient' response to treatment. Although removal of tumor followed by radiotherapy and temozolomide (TMZ)-based chemotherapy are the gold standard treatments, these strategies are unable to cope with heterogeneity, mutability, and invasiveness of GBM [14]. The highly invasive and infiltrating phenotype of GBM reduces the effectiveness of surgical resection to prevent eventual recurrences [15]. In addition, GBM patients frequently develop resistance to therapies, leading to relapse and poor survival rates [14,16]. Furthermore, anatomical inaccessibility of GBM complicates monitoring patients' responses to therapies, forcing clinicians to rely on tissue biopsies and MRI techniques [17,18]. Great efforts have been made to develop alternative strategies, including immunotherapy (i.e., blockade of immune-checkpoints, Antibody-Drug Conjugates (ADCs)-based targeted-therapy) or angiogenesis inhibitors [19,20], but unfortunately these new approaches have not improved patient responses or prevented therapy-resistance. Advances in early diagnosis and personalized medicine are urgently needed for improving outcomes in the treatment of glioblastoma and therefore the search for specific biomarkers together with new potential therapeutic targets will be crucial to achieve progresses in both diagnostic and therapeutic settings. Recently, liquid biopsies are emerging crucial in the discovery of cancer-related biomarkers and therapeutic targets, especially in GBM. Liquid biopsies can be used for diagnostic purposes,

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https://doi.org/10.1016/j.semcancer.2024.04.003
Received 1 December 2023; Received in revised form 19 March 2024; Accepted 30 April 2024
Available online 14 May 2024

but also for tumor evolution monitoring before and after patient treatments. Indeed, liquid biopsies offer a reliable platform for the evaluation of a variety of biomarkers, and are minimally invasive since they are based on body-fluids, such as blood or, as in the case of brain tumors, cerebrospinal fluid (CSF) [3,18]. Besides the evaluation of circulating tumor cells (CTCs), soluble proteins and microRNAs (miRNAs), all of which are highly susceptible to deterioration, extracellular vesicles (EVs) are recently becoming prominent as solid, multilevel sources through which to perform diagnosis and stratification to diagnose GBM or even stratify glioma patients [3,18,21]. At the same time, EVs are proving to be potential weapons for new ways of treating GBM, mainly due to their natural 'encapsulation capacity' of active molecules and for their ability to easily cross the blood-brain barrier (BBB) even when intact. In this context, EVs could act not only as diagnostic tools but also as means for the development of novel therapeutical approaches for GBM therapy.

2. Extracellular vesicles: multilayered nanocarriers

Acting as message carriers, EVs are emerging as crucial players both in physiological and pathological contexts due to their native properties and involvement in a plethora of mechanisms (i.e., cell-to-cell communications, immune responses, human reproduction [22–24]). In the physiological brain context, EVs exchange messages between neurons and glia supporting synaptic activity, neuroplasticity and exerting a neuroprotective role [25,26]. However, once in the tumoral context, the communication skills of EVs are exploited by tumor cells that handle EVs for their own ends, such as horizontal transfer of oncogenes or small nucleic acids, to influence both tumor and non-tumor cells in the TME. Ultimately this promotes tumor growth and progression, invasion, angiogenesis, drug resistance and polarization of immune responses [27–31]. Furthermore, EVs carry biological message even to distant sites since these vesicles are released into all body fluids (i.e., blood, urine, CSF). EVs are an heterogenous group of lipid-bilayer vesicles characterized by the expression of specific proteins (i.e., CD9, CD63, CD81, ALIX, TSG101, HSP70, HSP90, and others) [22,32] released potentially by all cells. They are generally classified into four major groups based to their size: exosomes (30–150 nm), microvesicles (MVs; 5–500 nm up to 1μm), apoptotic bodies (100–5000 nm), and large oncosomes (LO; 1–10μm) [33–35]. All these types of vesicles differ also in their biogenesis and cargo, which comprises a mixture of proteins, nucleic acids and metabolites representative of their cell of origin, that have a distinct functional impact on cellular mechanisms and cell behavior [27,33,36–38]. Although EVs-related research has notably increased in the last decades, the major weakness is represented by the lack of a standard isolation method, so optimization and standardization of EV-isolation approaches are urgently needed in order to improve the usefulness of EVs as tools for clinical purposes. Collectively, since EVs gather a cargo that is specific to the host cell, these small nanoparticles lend themselves as key features to identify the varying cell types that secrete these EVs. This is a critical characteristic that appoints EVs as principal sources of multilayered information for liquid biopsies, especially in GBM.

2.1. GBM-EVs: orchestrating the fates of tumor progression

It is widely assumed that cancer cells secrete EVs in higher quantities compared to normal cells [32,39]; a single GBM cell is able to secrete in the extracellular environment about 10'000 EVs carrying oncogenic molecules that can potentially affect recipient cells [40]. Many studies have attempted to elucidate the role of EVs in GBM (reviewed in [23,41–45]) and all the functions and the related molecular players revealed so far are summarized in Table 1. Essentially, EVs mediate an intense bidirectional dialogue between tumoral cells and all those cells heterogeneously composing the TME, such as stromal and glial cells, endothelial cells and pericytes, and resident immune cells [4,43]. Indeed, the GBM TME plays a crucial role in attracting mesenchymal stem cells (MSCs) [41] and immune infiltrating cells (i.e., TAMs, MDSCs) WHICH can potentially adopt tumor-supportive functions [46]. In this complex context, GBM cells use their EVs as a means either for their proliferative sustainment or to shape the surrounding environment in a way that is favorable for GBM growth [47]. This constant communication mediated by EVs in the TME plays an important role in tumor progression and in the shaping of TME as tumor supportive (Fig. 1).

In the recent years, tumor-derived EVs were found to be responsible for inducing GBM cells proliferation [48–63] and acting as pro-angiogenic effectors through the promotion of angiogenesis and sustainment of viability of endothelial cells [40,64–76], as well as by stimulating neovascularization processes within hypoxic regions [52,53,67,77–80]. In addition, GBM-EVs were found to finely shape the TME

Table 1
Table showing the most important GBM EVs-associated cargos (proteins and nucleic acids) identified for specific functions.

Functions	Proteins	Nucleic acids
Induction of proliferation, migratory, invasive phenotype, and radio-chemo resistance in GBM cells	Chloride Intracellular Channel-1 (CLIC1) [48]; EGFRvIII [49]; Suprabasin (SBSN) [51]; Glial water channel aquaporin-4 (AQP4) [58]; Notch1 [61]; Connexin 43 (Cx43) [79,110]; Macrophage migration inhibitory factor (MIF) [112]; Nicotinamide phosphoribosyltransferase (NAMPT) [125]	lncRNA HOTAIR [63]; circ-AHCY [59] /miR-148a [55]; circRNA 0001445 [56] /miR-221 [111]; lncRNA ROR1-AS1 [57]; linc01060 [50] / lncRNA AHIF [109]; miR-25–3p [91] /miR-27a-3p [113]; miR-1238 [114] /circ-METRN [117]; circATP8B4 [119] /miR-151a [120]; lnc-TALC [101] /circ-HIPK3 [122]; circ_0072083 [123] /circ_0043949 [121]; circCABIN1 [124] /miR-301a [126]; miR-106a-5p [127] /miR-30b-3p [128]
Induction of proliferative, inflammatory and immunosuppressive phenotype of microglia	N/A	miR-451/miR-21 [92]; miR-214–5p [93] / lncTALC [102]
Induction of angiogenesis, vascular development of endothelial cells and migration of pericytes	Vascular endothelial factor-A (VEGF-A) [65]	miR-21 [65] /miR-26a [66]; linc-CCAT2 [67] / linc-POU3F3 [68]; lncRNA HOTAIR [75]; miR-148a-3p [72] / miR-9–5p [69]
Induction of M2 macrophage polarization	Interleukine-6 (IL-6) [97]	miR-1246 [96] /miR-155–3p [97]; miR-6733–5p [98] / circNEIL3 [100]
Activation of MDSCs	Programmed Death-Ligand 1 (PD-L1) / Indoleamine 2,3-dioxygenase 1 (IDO1) [104]	miR-10a /miR-21 [102]; miR-1246 [103]
Induction of immunosuppressive phenotype of T cells	Programmed Death-Ligand 1 (PD-L1) [105,106]B7-H4 [107]	N/A
Metabolic reprogramming, induction of epithelial-to-mesenchymal transition fornormal astrocytes transformation in tumor-supportive cells	CD147 [88]	c-Myc CDSs /CCND3 mRNA [87]; RPS6 CDSs /MRPL51 CDSs [87]; Cytochrome c oxidase mRNA [87]; ENO1 mRNA/PGAM1 mRNA [87]; circ-AHCY [59] / lncRNA-ATB [89]

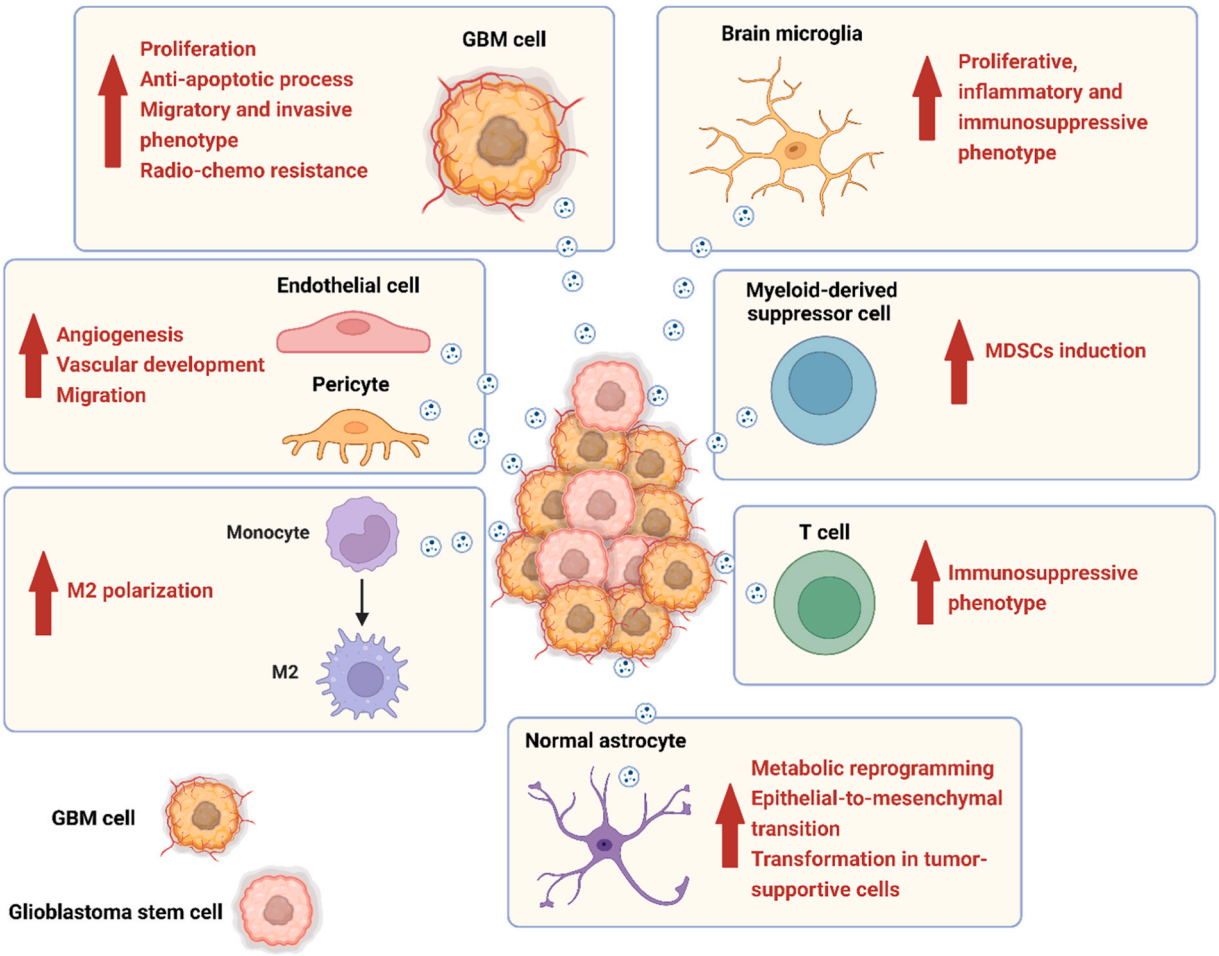

Fig. 1. *EVs functions in GBM microenvironment* Schematic representation of functions ascribed to GBM-released EVs in the context of tumor-stroma interaction.

not only in its non-cellular components (i.e., remodeling of extracellular matrix, migratory and invasive phenotypes of GBM cells [51,52,55,81–86]) but also by affecting cells populating or infiltrating into the tumor surroundings through the induction of proliferative [54,59,82,85,87–95], inflammatory [92–95], and immunosuppressive [96–108] traits. Furthermore, GBM vesicles were found to promote the acquisition of radio- and chemo-resistance traits in recipient GBM cells by transferring resistance-conferring cargo [63,84,109–130].

Collectively, the evidence collected so far strongly support the notion that the role of EVs and their contents in GBM tumors could have implications not only for understanding tumor biology but also for developing novel therapeutic strategies and identifying novel biomarker for diagnostic purposes.

3. GBM-EVs as robust reservoir of circulating biomarkers for liquid biopsies

Challenges regarding timely diagnosis, patient sampling, tumor progression as well as treatment response monitoring are still open doors in GBM clinical management. From this perspective, there is an impending need to find, validate, and employ novel GBM biomarkers for liquid biopsy to be used for early diagnosis, follow-up and personalized treatment. The biological fluids that can be employed as a source for liquid biopsy are cerebrospinal fluid (CSF) and peripheral blood derivatives (i.e., serum and plasma), both of which have advantages and disadvantages.

Indeed, while CSF offers the best source of brain-derived EVs, however, the lumbar puncture results in a highly invasive, distressing, and dolorous technique together with an elevated risk to contract cerebral infections [131,132]. Peripheral blood sampling is more accessible and appears to be more suitable in terms of monitoring, follow-up and personalized treatment tailored to each patient. However, tumor-derived EVs isolated from plasma are diluted and mixed with EVs of different derivation [132–134], causing a loss of specificity.

So far, a large number of valuable GBM biomarkers have been identified, ranging from proteins and nucleic acids to EVs' intrinsic morphological characteristics.

Sabbagh and co-workers have coined the term "vesiclemia" to indicate the concentration of EVs detected into plasma of GBM patients, that was reported to be specifically increased in GBM patients compared to healthy controls, as confirmed also by others [32,135–137]. This feature has exhibited solid reliability since a drop of vesiclemia parameter was observed after surgery or radiotherapy, whereas its increment was detected in recurrent GBM patients, suggesting how this specific parameter could reflect tumor burden or treatments response in GBM patients [135,136]. In addition, other morphological features of GBM EVs, including size, were reported to be different between tumor patients and healthy ones [137,138] though it seemed to be specific for plasma-derived EVs since saliva-derived EVs from pre- and post-surgery GBM patients displayed no significant differences [139].

Differences in EVs' cargo offer a wide variety of biological tools to detect GBM-related traits. *In vitro* studies have highlighted how EVs' content could potentially discriminate among GBM molecular subtypes [140–143], while proteome and miRnome of blood-derived EVs enabled stratification of glioma patients and to differentiate them from each other and also from other cancer specimens [111,144–148].

Unexpectedly, even circulating immune vesicles (CIVs) profiles, such as those of NK cells, were useful to classify among the different types of gliomas [149]. Besides shedding light on EVs roles in GBM, these techniques allowed the identification of differentially expressed proteins and coding or not RNAs conveyed by EVs, posing these molecules at the base of GBM diagnosis. Some of these novel biomarkers were proposed and employed for the detection of GBM given their abundance (or their lesser content) in EVs derived from either CSF or peripheral blood in comparison with healthy controls [40,55,63,64,114,136,142,144,146,150–158]. Numerous *in vitro* works have suggested other GBM-related molecules as potential novel biomarkers that need to be further evaluated in GBM patients [159–169]. The use of these biomarkers does not stop at the mere identification of GBM but also extends to the evaluation of the efficacy of surgery and/or chemo-radiotherapy such as in the case of testing the decrease in the levels of a specific biomarker [83,96,100,147,154,159,161,163,164,170–174]. In addition, biomarkers help also with the prediction of impending chemoresistance in GBM patients, including TMZ resistance [111,165,175–177]. Moreover, some specific GBM-related patterns have emerged as supportive for the identification of tumor progression alongside MRI analysis [170,178]. Finally, some of the molecules carried by GBM-EVs were confirmed to have also a prognostic significance, since often being associated with poor clinical outcome in GBM patients [71,172,177,179–181].

Nonetheless, in recent years other types of biomarkers, such as those detectable by metabolomics, are emerging. Although entirely preliminary, some works have highlighted noteworthy differences in metabolites content in GBM vesicles, proposing distinct metabolomic signatures, that pave the way for a novel and promising concept of biomarker. Indeed, specific profiles of metabolites were detected, allowing the discrimination among GBM subtypes [182] but also the exploration of these molecules in the profiling of GBM-related metabolic signature [183,184]; in relation with this, from the work of Bafiti and co-workers [185] a particular bioenergetic profile emerges after metabolomic investigations on plasma derived from GBM patients.

Although still exploratory, novel investigations are trying to decipher glycosylation signatures on the EVs surfaceoma in GBM, as done for other cancers [186,187]. Interestingly, distinct and aberrant glycosylation patterns of some proteins are emerging as able to differentiate cancer cells from the normal ones, making more worthwhile the consideration of these patterns for the development of novel biomarkers [187]. Preliminary studies have shown a typical pattern of the glycocalyx of GBM-derived EVs, characterized by enrichment in specific and complex glycosaminoglycans (GAGs), including heparan sulphate, chondroitin sulphate, dermatan sulphate, but also highly complex N-glycans, while small amount of high mannose glycans were represented [188–190]. Although not yet evaluated in circulating EVs from patients, glycosylation pattern seems to be a promising parameter to consider for further investigations aimed at the assessment of EVs as GBM biomarkers. Interestingly, already some highly glycosylated proteins have been considered to this scope, as in the case of CD147 that acquires a distinct glycosylation form on GBM-EVs that mechanistically is implicated in invasiveness of GBM cells [88]. Another highly glycosylated protein that was detected on EVs as a distinct, vesicular form of the protein is LGALS3BP. We and others first demonstrated that this protein is enriched in EVs from different derivations [191–195], and recently we showed how the vesicular but not the total circulating LGALS3BP is increased in serum of GBM patients [151], proposing this protein as a suitable biomarker for GBM detection based on liquid biopsy. Importantly, our data confirmed previous works where LGALS3BP was found to be correlated with glioma grade and with immunotherapy response [146,196]. In addition, this hyperglycosylated protein abundantly represented in GBM EVs lends as also a therapeutic target. Indeed, a maytansine derivative (i.e., DM3 or DM4)-based antibody drug-conjugate, namely 1959-sss/DM3 or 1959-sss/DM4 [191,197,198], showed promising and robust efficacy in GBM pre-clinical models employing patient-derived cell lines [151].

4. Therapeutic potential of EVs: nanocarriers for innovative GBM therapeutic strategies

EVs are emerging as innovative tools both as DDS or therapeutic strategies in the anti-cancer context. A growing number of studies have highlighted EVs' great potential by considering them as carriers that either could be functionalized to improve tropism for cancer cells or that could act as biomimetic coating for nanoparticles, ultimately resulting in a more efficient targeted therapy. In particular, the ability of these small vesicles to easily cross the BBB and to efficiently reach the brain tumor carrying their cargo, make EVs an attractive and eligible tool for therapeutic intentions especially for GBM treatment. Indeed, a wide variety of cargo through several loading strategies, could be potentially conveyed by EVs, as hydrophobic and hydrophilic chemo-drugs as well as inorganic-based nanoparticles or non-coding RNAs, as many studies have brought evidence for which they display high loading capability [199]. Hereafter, the different therapeutic strategies involving the use of EVs will be discussed and summarized in Table 2.

4.1. Anti-proliferative and pro-apoptotic effect

Evidence for which EVs themselves could have an intrinsic therapeutic potential have been brought by some works, as in the case of EVs isolated from MSCs of different derivation (adipose tissue, bone marrow, umbilical-chord) that showed tumor-impairing properties against GBM cells [200–202]. Other works have proposed native EVs as simple carriers for chemo-compounds by relying on their natural tropism for GBM tumor site. Several cytotoxic compounds were efficiently loaded and delivered through unmodified exosomes, such as the first-line anti-GBM drug TMZ in combination with antioxidant curcumin [203] or with inhibitor of PRMT5 (EPZ015666) [204]; with the chemotherapeutic agent vincristine (Vincr) [200], selumetinib (Selu) [205], or Atorvastatin (Ato) [206,207]. Interestingly, given that EVs naturally count in their cargo non-coding RNAs, many works have developed GBM therapeutic strategies by loading different miRNAs or anti-miRNA sponges into native exosomes (i.e., miR-124–3p, miR-512–5p, miR-124a, miRNA-584, miR-21-sponge) [208–212] or siRNAs (i.e., siMYC) [213] in order to regulate the expression of specific targets in GBM recipient tumor cells and induce potent anti-proliferative effects. Another work proposed MSC-derived exosomes to carry the transcript of an enzyme able to convert the prodrug 5-fluorocytosine (5-FC) into cytotoxic 5-fluorouracil (5-FU) as an innovative, non-toxic EVs-based approach [214]. However, only few works among these we have described so far have translated these EVs-based strategies for GBM treatment into pre-clinical models, suggesting how further investigations are needed to better promote EVs-based therapies for GBM.

4.2. Improvement of intracellular target drug delivery

EVs' surface was functionalized with a number of peptides in order to facilitate EVs' BBB transcytosis or to prolong their homing and accumulation within the tumor brain. One of the most used is the c(RGDyK) peptide that displays high affinity for $\alpha_v\beta_3$ integrin receptors overexpressed on actively proliferating endothelium of GBM tumor and also on GBM cells. c(RGDyK) functionalized EVs efficiently delivered doxorubicin [215,216], paclitaxel [217], but also siRNAs [218,219], and nanoparticles [220]; all of these tools resulted in prominent anti-tumor activity, confirming how much surface functionalization of EVs might be a crucial step to improve their therapeutic efficacy. EVs were also decorated with another BBB-penetrating peptide, angiopep-2 (Ang-2) peptide which is the ligand of lipoprotein receptor-related-1 (LRP-1), and it has been decisive in various studies [221–224]. Similarly, RGE peptide, that is the ligand of neuropilin-1 (NRP-1), overexpressed on both tumor endothelium and GBM cells, was used with the same purpose in several works [225–227]. T7-decorated EVs were also developed given the affinity of T7 peptide for transferrin receptor (TfR) highly

Table 2
Summary of reviewed EVs-based therapeutic tools in GBM.

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
Anti-proliferative and pro-apoptotic effect	EVs isolated from adipose tissue-derived mesenchymal stem cell **(ASC-EVs).**	ASC-EVs reduce the GBM cell proliferation and suppress tumor invasiveness and vascularization.	Cellular uptake and antiproliferative effect in HROG36, U87MG and T98G GBM cells.	Antitumor/anti angiogenic effect, and induction of anticancer gene expression in CAM model, based on the implantation of HROG36, U87MG and T98G cells on the chorioallantoic membrane of the developing chicken embryo.	[190]
	Exosomes isolated from rat bone marrow mesenchymal stem cells **(rBMMSCs).**	rBMMSCs-derived exosomes induce a reduction in the proliferation, migration, and invasion behavior of GBM cells.	Cellular uptake, migration/ invasion inhibition and cytotoxic effect of rBMMSCs-derived exosomes in C6 rat GBM cells.	-	[191]
	Vincr UC-MSC-EV: Mesenchymal stem cells derived from umbilical cord are used to produce EVs containing Vincristine.	Vincristine, a vinca alkaloid antineoplastic agent, is delivered using EVs isolated from UC-MSC.	Cytotoxic and pro apoptotic effect in U87MG GBM cells.	-	[189]
	U87 cells are used to produce exosomes containing curcumin or temozolomide (TMZ).	TMZ is a DNA alkylating agent approved by the FDA, while Curcumin is a plant polyphenolic compound with known antitumor effects. Exosomes released from drug-treated U87 cells is used to deliver drugs to GBM cells and to promote upregulation of apoptosis-related proteins.	Pro-apoptotic effect in U87 GBM cells.	-	[192]
	Small EVs isolated from GBM patients derived cell lines loaded with temozolomide (TMZ) or EPZ015666 through direct incubation.	EPZ015666 is an inhibitor of arginine methyltranferase-5 (PRMT5), overexpressed in GBM; loading of this drug or TMZ in small EVs from GBM patients derived cell lines improves selective delivery.	Antiproliferative effect in patient-derived GBM cells.	-	[193]
	U87MG-derived exosomes loaded with selumetinib by electroporation.	Selumetinib is a MAPK inhibitor active in neurofibromatosis type 1 (NF1)-associated glioblastomas, its loading in U87MG-derived exosomes confers tropism for GBM tumor tissue.	Cellular uptake and anticancer effect in U87 GBM cells.	Biodistribution and antitumor activity in U87 subcutaneous glioblastoma bearing mice model.	[194]
	AtoEXOs: Exosomes isolated from human derived endometrial mesenchymal stem cells (hEnMSCs) are loaded with atorvastatin through direct incubation.	Atorvastatin is a hydrophobic statin, which is shown to have pro-apoptotic and anti-angiogenic properties, while hEnMSCs-derived exosomes are used as carriers.	Effect on VEGF secretion and pro-apoptotic effect in U87MG GBM spheroids model.	-	[195]
	AtoEXOs: Exosomes isolated from human endometrial stem cells (hEnSCs-EXOs) are loaded with atorvastatin (ATO) through direct incubation.	EXOs isolated from human EnSC were used asa nano-carrier to load chemotherapeutic drug Ato, a statin with known antitumor capacities, for GBM treatment.	Cellular uptake and pro-apoptotic effect in U87 GBM cells and spheroids.	-	[196]
	Neural stem cells-derived exosomes (NSC-EXOs)loaded with miR-124–3p by electroporation.	NSC-EXOs are used as natural biological carriers of miR-124–3p whose overexpression inhibits GBM cell proliferation and migration by suppressing FLOT2 (flotillin 2)/AKT pathway and enhances chemosensitivity.	Cellular uptake, proapoptotic and migration/invasion inhibition effect in U87MG and U251MG GBM cells.	Antitumor activity in U87 subcutaneous glioblastoma bearing mice model.	[197]
	BMSC-miR-512–5p-Exo: Bone marrow mesenchymal stem cells are engineered in order to produce exosomes containing miR-512–5p.	BMSC exosomes delivers miR-512–5p to GBM, where it is normally downregulating, inducing tumor suppression by targeting JAG1, the most classic Notch ligand.	Cellular uptake, JAG1 downregulation and antiproliferative effect in U87 GBM cells.	Antitumor activity in orthotopic glioblastoma bearing mice model.	[198]
	Exo-miR124a: Mesenchymal stem cells (MSCs) cells are engineered to produce exosomes encapsulating miR124a.	miR-124a is an effective pan-GSC antiglioma miR during a screening and, when delivered by MSC-derived exosome, it downregulates Forkhead box (FOX)A2, a mediator of lipid metabolism and renders glioma stem cells (GSCs) unable to	Cytotoxic and anti-clonogenic effect in primary patient-derived GSCs.	Antitumor activity in an orthotopic patient-derived GSCs-based bearing mice model.	[199]

(*continued on next page*)

Table 2 (*continued*)

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
		efficiently metabolize lipids, reducing its viability.			
	EV-584: Mesenchymal stem cells (MSCs) cells are engineered to produce exosomes encapsulating miRNA-584.	MSC-derived exosomes are used to deliver miRNA-584, a known tumor suppressor which binds the3'-UTR of CYP2J2 and reduces MMP-2 expression, inducing tumor growth and metastasis inhibition.	MMP-2 downregulation and pro apoptotic effect in U87 GBM cells.	Antitumor activity in U87 subcutaneous glioblastoma bearing mice model.	[200]
	miR-21-Sponge Exosomes:293 T cells are engineered to produce exosomes encapsulating miR-21-sponge.	miR-21 is a well-known miRNA proposed as a suitable target for GBM therapy, and its inhibition via miR-21-sponge induces several antitumoral and chemo sensitizing effects.	MiR21 inhibition and pro-apoptotic effect in U87MG and C6 GBM cells.	Antitumor activity in the C6 orthotopic glioblastoma bearing rat model.	[201]
	iExo-Myc: Mesenchymal stem cells-derived exosomes loaded by electroporation with siRNA targeting Myc.	MSC-derived exosomes are used to pass BBB and deliver siMyc, which silences Myc, whose overexpression is required for GBM progression and maintenance.	-	Antitumor activity via intravenous/intranasal administration in the U87 orthotopic glioblastoma bearing mice model.	[202]
	yCD::UPRT-MSC-exosomes: Mesenchymal stem cells (MSCs) from various derivation are engineered to have integrated transcriptional active yeast cytosine deaminase (CD):: uracilphosphoribosyl transferase fusion gene (yCD::UPRT).	MSC-derived EVs carrying mRNA of the enzyme CD::UPRT, which catalyzesthe conversion of noncytotoxic pro drug 5-fluorocytosine (5-FC) into cytotoxic 5-fluorouracil(5-FU), are able to migrate to tumors and inhibit tumor growth inducing GBM cells to perform 5-FC conversion.	Cytotoxicity of yCD::UPRT-MSC-exosomes used in the form of Conditioned Medium in combination with prodrug 5-FC in C6 rat GBM cells.	Antitumoractivity of yCD:: UPRT-MSC-exosomes used in the form of Conditioned Medium in combination with 5-FC in the C6 orthotopic glioblastoma bearing rat model.	[203]
	T7-siYY1-exo:293 T cells are engineered to produce exosomes expressing T7 peptide and are loaded with cholesterol-modified siYY1 (Yin Yang 1) by electroporation.	YY1 is a transcription factor overexpressed in GBM involved in cell dedifferentiation, cell survival and therapeutic resistance, and it is silenced by siRNA delivered with EVs expressing T7, a transferrin receptor (TfR) binding peptide which promotes exosomes uptake by both cerebral vascular endothelial and GBM cells.	BBB transcytosis, cellular uptake, and cytotoxicity also in combination with Temozolomide and radiotherapy in LN229 GBM cells and tumor-spheroids.	Biodistribution and antitumor activity of T7-siYY1-exo as single agent and in combination with TMZ/radiotherapy on the LN229 and patient-derived orthotopic glioblastoma bearing mice model.	[216]
Improvement of intracellular target drug delivery	**Dox@cRGDyC-sEVs:**U87-derived sEVs loaded with Doxorubicin by pH-dependent incubation and functionalized with cyclic arginine-glycine-aspartic acid-tyrosine-cysteine peptide (cRGDyC) through DSPE-mPEG2000-maleimide via a thiol-maleimide coupling reaction.	cRGDyC is a ligand for integrin αvβ3 overexpressed by cerebro-microvascular endothelial and GBM cells, so it confers targeting ability to sEVs containing Dox.	Cellular uptake, intracellular trafficking and cytotoxic activity in U87 GBM cells.	-	[204]
	cRGD-Exo-PTX: Exosomes isolated from embryonic stem cells (ESCs) are modified on the surface with (cRGDyK) peptide and loaded with paclitaxel (PTX) by direct incubation.	Direct modification ofexosomes surface with tumor-targeting ligand (cRGDyK) isefficient in enhancing tumor retention of exosomes by binding αvβ3 integrin receptors over-expressed onthe surface of actively proliferating endothelium of GBM tumor tissues, and improves tumor delivery of the mitotic inhibitor PTX.	Cellular uptake and pro-apoptotic effect in U87 and U251 GBM cells.	Biodistribution and antitumor activity in the U87 orthotopic and subcutaneous glioblastoma bearing mice model.	[206]
	RGD-EVs:293 T cells are engineered to produce exosomes expressing elevate levels of RGD peptide on the surface and then loaded with Doxorubicin or siRNA.	Functionalization of EVs with RGD peptide, which binds integrins, improves delivery to GBM cells of Dox or siRNA.	Cellular uptake and Dox cytotoxic effect in U87 and HROG36 GBM cells.	-	[205]
Photothermal therapy	**R-exo-ICG:**U87MG derived exosomes loaded with Indocyanine green (ICG) by electroporation and conjugated with RGE peptide.	ICG is a clinical near-infrared fluorescent dye possessing photodynamic/photothermal capacities; its loading in U87MG-derived exosomes modified with RGE peptide, a neuropilin-1(NRP-1) targeted peptide, increases cell uptake	Cellular uptake and anticancer effect in combination with laser irradiation in U87MG GBM cells.	Biodistribution and antitumor activity in U87MG subcutaneous glioblastoma bearing mice model.	[213]

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Table 2 (*continued*)

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
		and induces cell apoptosis after laser irradiation.			
	ICG/PTX@RGE-EV:EVs isolated from Raw264.7 cells are modified RGE peptide on the membrane and loaded with Paclitaxel (PTX) and indocyanine green (ICG) by electroporation.	RGE is used in order to increase penetration, while combination of the chemotherapeutic activity of PTX and photothermal capacities of ICG are used.	Cellular uptake and pro-apoptotic effect in combination with laser irradiation in U251 GBM cells.	Biodistribution, PTX release and antitumor activity in combination with laser irradiation in the U251 orthotopic glioblastoma bearing mice model.	[214]
Photodynamic therapy	**[bEV(TPP-Ce6)] :** triphenylphosphonium (TPP) linked to chlorin e6 (Ce6) *via* an ester linkage is incapsulated in brain endothelial (bEnd.3) cell-derived EVs (bEVs).	TPP, a positively charged lipophilic mitochondria-targeting agent, linked to the Ce6 photosensitizer is able after light irradiation to induce apoptosis through mitochondria-targeted photodynamic therapy. Loading of these agents in bEVs makes them capable of penetrate BBB for their intrinsic transferrin receptor-mediated transcytosis capacity.	Cellular and mitochondrial uptake, ROS production and apoptosis induction after light irradiation in U87MG GBM cells.	Biodistribution and antitumor activity in association with light irradiation on the U87MG orthotopic glioblastoma bearing mice model.	[220]
	HCQ@ZnS@eRGD:hollow zinc sulfide (ZnS) nanoparticles loaded with hydroxychloroquine (HCQ) and covered by a shell of dual-stimuli responsive hybrid exosome containing exosome with pH- and redox-responsive iRGD ligand.	On one side, Zns acts as a photosensitizer for reactive oxygen species (ROS) production to damage organelles in GBM cells; while HCQ inhibits autophagic flux, by promoting accumulation of impaired organelles. In order to increase efficiency for crossing BBB and capability to target GBM cells, shell of nanoparticles is coated with U87-derived exosomes and functionalized with the cell membrane penetration peptide iRGD.	Uptake, ROS production and autophagic flux blockage in U87 GBM cells.	Biodistribution and anti-tumor efficacy in association to light irradiation on the U87 orthotopic glioblastoma bearing mice model.	[208]
Sonodynamic therapy	**CSI@Ex-A:**CSI are fabricated by encapsulating catalase (CAT) into GSH-responsive silica nanoparticles (CAT@SiO_2) and then loaded with the sonosensitizer indocyanine green (ICG). CSI are further coated with AS1411 aptamer-modified macrophage-derived exosomes (Ex-A).	High GSH expression of the tumor site triggers biodegradation of the nanoplatform and the released CAT catalyzes conversion of endogenous hydrogen peroxide (H_2O_2) to oxygen relieving tumor hypoxia. In addition, GSH depletion and O_2 self-supply effectively enhanced the sonodynamic therapy efficiency thanks also to the sonosensitizer ICG. Coating with AS1411 aptamer-modified macrophage-derived exosomes is used to achieve BBB penetration and tumor site accumulation.	BBB transcytosis, cellular uptake, hypoxia degree induction and cytotoxic activity in U87 GBM cells and 3D spheroids.	BBB penetration, biodistribution and antitumor activity in association with ultrasound irradiation on the U87 orthotopic glioblastoma bearing mice model.	[217]
Ultrasound-based therapy	**R-Exos-Dox /B-Exos-Dox:**EVs isolated from murine macrophage Raw264.7 (R-Exo) or from mouse blood (B-Exo) and loaded with Doxorubicin by direct incubation.	Focused ultrasound (FUS), a non invasive strategy that can produce transient, reversible, and local BBB disruption, is used to increase the targeted delivery of R-Exos-Dox /B-Exos-Dox.	Cellular uptake, cytotoxic effect and ultrasound-promoted BBB transcytosis in GL261 GBM cells.	Ultrasound promoted BBB penetration, biodistribution and antitumor activity in the GL261 orthotopic glioblastoma bearing mice model.	[221]
SPION-based therapy	**RGE-Exo-SPION/Cur:**Macrophage-derived exosomes are conjugated to RGE peptide by click chemistry and loaded with superparamagnetic iron oxide nanoparticles (SPIONs) and Curcumin (Cur) by electroporation.	RGE is a neuropilin-1(NRP-1) targeted peptide used for its ability to penetrate tumor tissue; while cytotoxic effect is entrusted to Cur, a plant polyphenolic compound with known antitumor effects and to magnetic fluid hyperthermia (MFH) induced by SPIONs usage.	Cellular uptake and anticancer effect in U251 and Bel-7404 GBM cells.	Biodistribution and antitumor activity on the U251 orthotopic glioblastoma bearing mice model.	[212]
Boron neutron capture therapy	**BCD-Exos:**Boron-containing carbon dots (BCDs) constituted of D-glucose and boron phenylalanine (BPA) are incapsulated in macrophage-derived exosomes.	Carbon dots are responsible of Boron Neutron Capture Therapy (BNCT), a radiation-based strategy based on the selectively concentration of boron compounds in tumour cells and application of epithermal	Cellular uptake in U87MG GBM cells.	BBB penetration and antitumor activity in association with the thermal neutron beam irradiation on the U87MG orthotopic glioblastoma bearing mice model.	[222]

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Table 2 (*continued*)

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
		neutron beam radiation. The coating of the BCDs with macrophage-derived exosomes (BCD–Exos) is exploited to prolong retention time and enhance accumulation in tumor tissue.			
Ferroptosis therapy	**Ang/TAT-sgGSS-EVs:**293 T cells are engineered to produce exosomes expressing Angiopeptin-2 (Ang) and trans-activator of the transcription (TAT) peptide on the surface, in which Cas9 protein/sgRNA complex to deplete glutathione synthetase (GSS) is loaded.	These dual modified functional EVs uses Ang (with high affinity for overexpressed LRP-1) and the potent cell penetrating TAT peptides in order to encapsulating and protecting the sgRNA and Cas9 protein for GSS non invasive knockout. Deletion of GSS impairs the synthesis ofGSH, and this results in the inactivation of glutathione peroxidase 4 (GPX4) and iron accumulation, thereby causing lipid peroxidation-mediated ferroptosis.	BBB transcytosis, cellular uptake, penetrating and genome-editing efficiency, and cytotoxicity also in combination with radiotherapy in LN229 GBM cells and patient-derived organoids.	Biodistribution and antitumor activity of Ang/TAT-sgGSS-EVs as single agent and in combination with radiotherapy on the LN229 and patient-derived orthotopic glioblastoma bearing mice model.	[211]
	MNP@BQR@ANG-EXO-siGPX4: hMSC-derived exosomes loaded with siRNA of glutathione peroxidase 4 (GPX4), are engineered to express into the membrane the Angiopep-2 targeting peptide. These modified exosomes are conjugated taking advantage of CD63 antibody to modified core–shell NPs consisting of Fe_3O_4 nanoparticles@ mesoporous silica (Fe_3O_4@$mSiO_2$ NPs, MNPs), which are functionalized with brequinar (BQR).	After the application of an external local magnetic field, the MNP@BQR@ANG-EXO-siGPX4 accumulate in brain blood vessels and penetrate the BBB by recognition of LRP-1 from the ANG targeting peptide. Synergistic GBM treatment based on ferroptosis induction is achieved through the simultaneous knockdown of GPX4 and DHODH inhibition from BRQ, and Fe_3O_4 NPs-mediated Fe^{2+} release.	Cellular uptake and enhancement of ferroptosis in A172 and LN229 GBM cells.	Biodistribution and antitumor activity with the application of a local magnetic field on the LN229 orthotopic glioblastoma bearing mice model.	[209]
Immunotherapy	**T7-Exo/siGalectin-9:**T7 peptide-decorated exosomes derived from 293 T cells are loaded with Galectin-9 siRNA by electroporation.	T7 is a seven-peptide ligand of transferrin receptor which improves GBM drug delivery; besides Galectin-9 downregulation can promote the M1 polarization of macrophages, which are able to induce the phagocytosis of GBM cells. T7-Exo/siGalectin-9 enhance also the anti-tumor immune response of CD8+ T cells on GBM cells.	Cellular uptake and delivery of Galectin-9 siRNA effect in SHG-44 GBM cells.	-	[215]
	R-EXO-T/D:GL-261 cell-derived exosomes are reassembled through removal of DNA and protein cargo by ultrasonic fragmentation; then temozolomide (TMZ) and dihydrotanshinone (DHT) are co-incapsulated in R-EXO by direct incubation.	TMZ exhibits antitumor activity by methylating DNA molecule and interfering their replication, while DHT comes from traditional Chinese medicine and it promotes tumor cell apoptosis by up-regulating caspase-3, but importantly also reduces TMZ resistance by down-regulating MGMT and P-gp expression. Their antitumor effect is added to intrinsic immunostimulant properties of reassembled glioma-derived exosomes.	Cellular uptake and anticancer effect in U87 and GL261 GBM cells; immune stimulatory effect in monocytes/macrophages.	BBB penetration and antitumor activity on the orthotopic glioblastoma bearing mice model.	[224]
	CpG-EXO/TGM: Tanshinone IIA-Glycyrrhizic acid micelles (TanIIA-GL TGM) constructed with self-assembly strategy and loaded into serum-derived EXO membranes, CpG ODN 1826 oligonucleotide is anchored on the EXO membrane.	TanIIA and GL TGM are STAT3 inhibitors derived from traditional Chinese medicine and induces cell apoptosis, while CpG ODN 1826 acts as an agonist of Toll-like receptor 9 and induces immature DCs conversion in mature DCs and M2-TAMs polarization to M1-TAMs. Usage of EXO membranes permits the TfR-mediated delivery to GBM tissue.	BBB transcytosis, cellular uptake, 3D GBM spheroid penetration, immunostimulatory and cytotoxic activity in GL261 GBM cells.	Biodistribution, antitumor efficacy as single agent and in combination with TMZ, and anti-GBM recurrence effect on the GL261 orthotopic glioblastoma bearing mice model.	[225]

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Table 2 (*continued*)

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
	EV(CpG-STAT3ASOCy3): Neural stem cells (NCS)-derived exosomes encapsulating CpG-STAT3ASO conjugate, composed of antisense oligonucleotides (ASOs) targeting STAT3 and CpG oligodeoxynucleotides (ODNs).	CpG-STAT3ASO conjugates are naturally integrated in exosomes by NSCs, which, by inhibiting STAT3, stimulates immune activity of dendritic cells/ macrophages inducing nuclear factor Kb (NF-Kb) signaling and IL-12 production.	Immunostimulatory effect, cellular uptake and migration inhibition in GBM-associated immune cells and U251 GBM cells.	Biodistribution, tumor immune infiltrate analysis and antitumor activity in the GL261 orthotopic and subcutaneous glioblastoma bearing mice model.	[226]
	RGD-EV:siPDL1:EVs isolated from ReNcell VM (ReN) cells, a neural progenitor cell line derived from the ventral mesencephalon region of the human fetal brain, are chemically modified with the tumor-targeting c (RGDyK) peptide, and loaded by direct incubation with cholesterol-modified siPD-L1.	RGD peptides are well-known ligands that bind integrin αvβ3 used to permit delivery of siPD-L1. Increasing expression of PD-L1 is involved in impairment of antitumor immunity in response to radiotherapy. So the proposed mechanism postulates that a burst of radiation can enhance the targeting efficiency of RGD-EVs to brain tumors, while the combination of PD-L1 inhibition provides an increased benefit for GBM treatment.	-	Biodistribution, PD-L1 downregulation, tumor immune infiltrate analysis and antitumor activity in combination with radiotherapy in the GL261 orthotopic glioblastoma bearing mice model.	[207]
	Co-delivery of tumor-derived exosomes (from C6 rat glioblastoma cells) with ***α***-galactosylceramide (***α***-GalCer) – pulsed dendritic cells (DCs).	Dendritic cells (DCs) are the most powerful antigen-presenting cells, so they are used for vaccine-based therapy here withco-delivered tumor-derived exosomes as antigen source and DCs pulsed with a potent synthetic invariant natural killer T (iNKT) agonist, α-GalCer, which is able to enhance T cell responses by encouraging iNKT: DC interactions.	-	Antitumor activity, T lymphocyte cytotoxicity induction and cytokines secretion in the C6 orthotopic glioblastoma bearing rat model.	[227]
Chemosensitizing therapy	**EXO-An2-Apt:**Exosome isolated from THP-1 cells are loaded with Temozolomide (TMZ) or O^6-benzylguanine (BG) by sonication. Then they are functionalized with target ligands angiopep-2 (An2) and CD133 RNA aptamers (Apt) via an amphiphilic molecule bridge.	TMZ is the first-line anti GBM drug and DNA repair protein O^6-alkylguanine-DNA alkyltransferase (AGT) can induce TMZ resistance, which is inhibited by BG. These two drugs are incapsulated in dual-receptor-specific exosomes, which are functionalized with An2, a specific ligand of LRP-1, and an RNA aptamer against CD133, receptor expressed by glioblastoma stem cells (GSC) for enhancing GBM/GSC cell targeting and BBB permeation.	Cellular uptake, and cytotoxic effect in U87MG GBM cells and GSC.	Biodistribution and antitumor activity on the U87MG orthotopic glioblastoma bearing mice model.	[210]
	ANG-EXO:293 T cells are engineered to produce exosome expressing Angiopetin-2 peptide on the surface, then multi-siRNAs containing the sequences corresponding to si-circCABIN1 and si-OLFML3 were loaded into exosomes by electroporation.	CircCABIN1 RNAis highly expressed in GBM, important for the self-renewal maintenance of GSCs to initiate acquired resistance by regulating the expression of olfactomedin-like 3 (OLFML3). Moreover, upregulation of OLFML3 activates the ErbB signaling pathway and ultimately contributes to stemness reprogramming and TMZ resistance.Cholesterol-modifiedmulti-siRNA, which simultaneously suppressed circ-CABIN1 and OLFML3 expression, are driven to the tumor using exosomes expressing tumor-targeting peptide ANG.	BBB transcytosis and Temozolomide sensitization in LN229 GBM cells.	BBB penetration and antitumor activity as single agent and in combination with TMZ on the orthotopic glioblastoma bearing mice model.	[124]
	HSSP-BMSC$_{Exo}$-TMZ/ HSSP-BMSC$_{Exo}$-siRNA: Exosome isolated from bone marrow mesenchymal stem cells (BSMCs) are decorated with heme oxygenase-1 (HMOX-1) specific short peptide (HSSP) and	The signal transducer and activator of transcription 3 (STAT3) is responsible for TMZ resistance in GBM via regulating the expression of O_6-methylguanine DNA methyltransferase (MGMT), so	BBB transcytosis, cellular uptake, and TMZ sensitization in U251 GBM cells.	BBB penetration, biodistribution and antitumor activity on the U251 orthotopic glioblastoma bearing mice model.	[228]

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Table 2 (*continued*)

Therapeutic strategy	Composition of EVs-based tool	Proposed mechanism of action	*In vitro* assays	*In vivo* assays	Ref
	loaded with Temozolomide or siSTAT3 by sonication.	downregulation of the STAT3 not only can induce apoptosis in the cancer cell but also is capable of restoring TMZ sensitivity.HMOX1 represents a cell-surface membrane protein signature for GBM, in particular for TMZ resistant GBM cells, so HSSP expression on $BMSC_{Exo}$ improves specific target delivery of TMZ and siSTAT3.			
	CXCR4-NSC-mpEVs:Microvesicles isolated from neural stem cells (NSCs) are engineered to overexpress on their surface the C-X-C chemokine receptor type 4 (CXCR4); then they are loaded with antimiRNA-21 and miRNA-100 using a scalable microfluidic platform.	CXCR4 is an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1), overexpressed in GBM cancer cells used to increase tumor delivery of miRNA loaded EVs. miRNA-21 is anoncomiRNA overexpressed in most GBMs, involved ingliomagenesis, invasion, metastasis, and regulating apoptosis and drug-resistance pathways; while miRNA-100 is downregulated in GBM, resulting in tumorigenesis. Combining anti-miRNA-21 and miRNA-100 could be an advantageous therapeutic strategy to improve the effects of TMZ.	Cellular uptake and TMZ sensitization in GL26 and U87MG GBM cells.	Biodistribution and antitumor activity in combination with TMZ in the GL26 orthotopic glioblastoma bearing mice model through intranasal delivery.	[229]

expressed on endothelial cells [228,229]. Finally, RNA aptamers were anchored to EVs as a targeted delivery strategy as in the case of AS1411 aptamer [230] or CD133 RNA aptamer [222].

4.3. Photothermal and photodynamic therapies

In the context of innovative and recently emerging approaches, some works have proposed EVs as nanocarriers for their application in photodynamic (PDT) and photothermal (PTT) therapies. These two highly tissue penetrative approaches utilize photosensitizing or photothermal compounds that when subjected to a particular wavelength or to light irradiation lead to harmful effects for cells through different mechanisms [231,232]. Given their non-specific nature, loading these compounds onto EVs represents a valid approach to render GBM-specific these promising approaches. In the context of PTT, targeted GBM-derived exosomes were chosen to carry the fluorescent dye indocyanine green (ICG) (R-exo-ICG) that gave significant results *in vivo* in terms of tumor accumulation and therapeutic activity in orthotopic models [226]. ICG was also loaded together with paclitaxel (PTX) onto RGE-modified murine macrophage-derived EVs to obtain ICG/PTX@RGE-EV showing potent photothermal properties upon laser irradiation in U251 GBM *in vitro* and *in vivo* orthotopic model in absence of relevant side effects [227]. Regarding PDT application, photosensitizer chlorin e6 (Ce6) linked to the mitochondria-targeting agent triphenylphosphonium (TPP) were stably conveyed by brain endothelial cell-derived EVs (bEVs) to induce ROS production and mitochondrial damage in GBM cells upon light irradiation. This strategy led to a significant tumor shrinkage and a favorable biodistribution in orthotopic GBM-xenografted treated mice in absence of PDT-related side effects [233]. Hollow zinc sulfide (ZnS) nanoparticles, functioning as photosensitizers, were loaded with the autophagic inhibitor hydroxychloroquine (HCQ) to obtain a synergistic effect for PDT application, and covered by GBM-targeting U87-derived exosomes. These HCQ@ZnS@eRGD vesicles showed increased tumor accumulation and a prominent tumor shrinkage in orthotopic model [220]. Collectively, these works highlight how PDT could be a promising approach to develop further in GBM therapy context.

4.4. Sonodynamic and FUS therapies

In the scenario of these innovative approaches for the treatment of GBM, sonodynamic therapy (SDT) is emerging as a novel therapeutic modality by combining ultrasound-based stimuli with ROS-mediated anti-cancer mechanisms. CSI@Ex-A are composed of an inner core of catalase-containing GSH-responsive silica nanoparticles (CSI), and a coating of macrophages-isolated exosomes (Ex-A) modified with the sonosensitizer ICG. CSI@Ex-A vesicles are particularly effective in *in vivo* orthotopic GBM model after ultrasound stimuli [230]. Focused ultrasound (FUS), relying on its ability to temporarily damage BBB, used in combination with doxorubicin (Dox)-based chemotherapy delivered by macrophage-derived (R-Exos-Dox) and blood serum-derived exosomes (B-Exos-Dox), improved *in vitro* and *in vivo* BBB transcytosis [234].

4.5. SPION-based and BNCT therapies

Superparamagnetic iron oxide nanoparticles (SPIONs), initially developed with diagnostic purposes, loaded with Curcumin onto GBM-targeted exosomes (RGE-Exo-SPION/Cur) improved their specificity for GBM cells and provided strong evidence for their potent anti-GBM effectiveness since tumor shrinkage was observed in orthotopic GBM-xenografted mice treated [225]. Similarly, also boron neutron capture therapy (BNCT) was further implemented by using EVs as carriers for both diagnostic and therapeutic aims. BNCT is a non-invasive radiation therapeutic approach relying on boron-based compounds subjected to thermal neutron beam radiation, ideally in a focused and local manner, leading to fission reaction of ^{10}B and ultimately to cell lysis. Li and collaborators coated boron-containing carbon dots (BCDs), constituted of boron phenylalanine (BPA), with exosomes derived from circulating macrophages (BCD-Exos) to prolong retention at the tumor site. BCD-Exos treated orthotopic GBM-xenografted mice showed complete tumor remission, even though biodistribution was not favorable [235].

4.6. Ferroptosis therapy

Ferroptosis, a recently discovered iron-dependent cell death, is

triggered by excessive lipid peroxidation of cell membranes and it is finely regulated by several defense systems, such as GSH-GSH peroxidase 4 (GPX4) axis or the mitochondrial dihydroorotate dehydrogenase (DHODH) [236]. Li and collaborators developed complex nanocarriers composed of magnetic nanoparticles (MNPs) constituted of a ferrous core loaded with DHODH-inhibitor brequinar (BQR), conjugated via CD63-recognition to GBM-targeting hMSC-derived exosomes carrying siGPX4 (MNP@ANG-EXO-siGPX4@BQR). This combination achieves a triple action against GBM by simultaneously impairing DHODH and GPX4 ferroptosis defense systems and releasing ferrous ions to trigger ferroptosis, resulting in an *in vivo* prominent impairment of tumor progression and significant prolonged survival [221]. Another therapeutic strategy based on the induction of ferroptosis was proposed by developing a CRISPR/Cas9-based *in vivo* gene editing platform carried by GBM-targeting exosomes to specifically delete glutathione synthetase (GSS), associated with the suppression of radiotherapy-induced ferroptosis in GBM cells. Ang/TAT functionalized sgGSS-EVs strongly sensitize GBM cells to radiotherapy through triggering ferroptosis as demonstrated by the potent reduction in tumor volumes observed in both LN229-bearing and patient-derived GSC-bearing mice [224].

4.7. Immunotherapy

As widely discussed in the previous paragraphs, GBM is one of the coldest tumors in humans and this is mainly due to its well-defended BBB-mediated isolation and to immune evasion mechanisms. This is the reason for which EVs-based immuno-therapies were designed as alternative therapeutic strategies for GBM treatment. To induce TAMs polarization towards M1 phenotype and restrict GBM immunosuppressive environment, GBM-targeting exosomes loaded with siRNA for galectin-9 (T7-Exo/siGalectin-9) were employed to induce the activation of TLR5-IRF5 pathway involved in M1 re-polarization processes, with only *in vitro* results [228]. In this context, murine GBM derived-exosomes, emptied of their original cargo were loaded with TMZ (T) and dihydrotanshinone (DHT or D), helpful in reversing TMZ-resistance. They showed *in vitro* immunostimulatory properties and *in vivo* anti-tumor efficacy [237]. Immunoadjuvant as CpG oligonucleotides can be used to stimulate dendritic cells or reprogram TAMs in the GBM TME via toll-like receptor 9 (TLR-9), as Cui and collaborators proposed with CpG-modified serum-derived exosomes encapsulating self-assembled Tanshinone IIA-Glycyrrhizic acid micelles (TanIIA-GL TGM), which are STAT3 inhibitors. When CpG-EXO/TGM vesicles were administered in orthotopic GBM-bearing mice, prominent tumor reduction was observed, associated with DCs and cytotoxic T-cells activation, M1 TAMs polarization and immunosuppressive Tregs decrease in the TME ascribable to CpG effect. Moreover, CpG-EXO/TGM treatment was applied also in combination with TMZ leading to a significant tumor shrinkage and extended survival rate, further underlining the efficacy of the EVs-based immuno-chemotherapy proposed in this study. In addition, this therapeutic strategy was also proposed for anti-GBM recurrence effect in an experimental post-operative setting in which CpG-EXO/TGM-treated mice recovered faster than animals treated with only EXO/TGM, but importantly both these therapies reduced residual tumor and prevented its restarting [238]. A variant of the previous immunoadjuvant, the CpG-STAT3ASO conjugates, consisting of the TLR9-targeting CpG oligo together with the STAT3-targeting antisense oligo, were shown to display immunostimulatory properties in a more regulated and targeted manner when naturally encapsulated into NSC-derived exosomes (EV(CpG-STAT3ASO)). EV(CpG-STAT3ASO) are able to induce DCs and macrophages activation *in vitro,* besides to the inhibition of tumor progression observed in a subcutaneous GBM-xenografted model [239]. Immunotherapy based on the combination of radiotherapy and delivery of siPD-L1, to mediate immune check-point blockade, was proposed to counteract the radiation-induced increase of PD-L1 expression levels occurring on tumor and TME cells. A burst of radiation coupled with the administration of siPD-L1-loaded exosomes derived from embryonic neuronal progenitors (RGD-EV) efficiently improved the accumulation of these vesicles within brain tumor and consequently provoked a massive immune cells infiltration within the immunological cold GBM tumor, beside to a potent tumor growth inhibition [218].These data all converge into the idea of an EVs-based immunotherapy that can robustly synergize with consolidated radiation schedules for GBM treatment.

In the context of immunotherapies, an innovative approach corresponds to dendritic cell (DC)-based vaccines as the one brought by Liu and collaborators. The therapeutic strategy proposed in this study contemplates DC loaded with α-galactosylceramide (α-GalCer), which is a potent synthetic invariant natural killer T (iNKT) agonist able to enhance T cell responses by encouraging iNKT:DC interactions, together with rat GBM-derived exosomes as source of tumor-associated antigens (TAAs), instead of tumor lysates. This complex strategy resulted in significant suppression of tumor growth associated with an extended survival of orthotopic GBM-bearing rats and an increase of infiltrating T lymphocytes [240].

4.8. Chemosensitizing therapy

Given that resistance is one of the major challenges in GBM progression, EVs were also used in therapeutic strategies aimed at sensitizing GBM and GSC cells, which often are the source of resistance-related mechanisms, to radio and chemotherapy. With this aim, for the eradication of TMZ-resistant GBM cells, TMZ and O_6-benzylguanine (BG), used as enhancer of TMZ activity, were loaded onto macrophage-derived functionalized exosomes (EXO-An2-Apt-TMZ/BG). The administration of EXO-An2-Apt-TMZ/BG resulted in a significant anti-tumor efficacy in orthotopic GBM-bearing mice [222]. As an alternative strategy to reverse TMZ-resistance in GBM cells, GBM-targeting exosomes were loaded with a multi-siRNA to specifically silence circCABIN1 and olfactomedin-like 3 (OLFML3), which were demonstrated to be involved in GBM TMZ-resistance related mechanisms. Ang-multi-siRNA-EXO combined with TMZ successfully resulted in the most effective condition in term of tumor growth inhibition in GBM orthotopic mice compared to TMZ alone [223]. In another work, Rehman and collaborators proposed a combination therapy based on the fine-tuned targeted delivery of TMZ and siRNA targeting STAT3, which acts as a promoter of TMZ resistance in GBM, by using $BMSC_{Exo}$ decorated with heme-oxygenase-1 (HMOX1) specific short peptide (HSSP) to improve GBM specificity, thus obtaining HSSP-$BMSC_{Exo}$-TMZ and HSSP-$BMSC_{Exo}$-siSTAT3. In this way, TMZ-sensitivity was restored in TMZ-resistant GBM cells since it was observed a significant tumor impairment in an orthotopic, TMZ-resistant GBM mouse model. Moreover, this proposed EVs-based treatment prolonged survival and did not exhibit serious adverse effects on mice treated, proposing a biocompatible and effective therapeutic nanoplatform for resistant GBM [241]. Another alternative to sensitize resistant GBM cells was reported by a study in which miR-100 (downregulated in GBM) and anti-miR21 (overexpressed in GBM) were loaded into CXCR4-expressing NSC-derived vesicles, also labeled with ICG for imaging purposes. These vesicles (mpEVs) efficiently delivered through intra-nasally administration, were able to sensitize GBM in the perspective of a TMZ combination therapy. This approach resulted in a prominent tumor regression and improved overall survival in an orthotopic GBM mouse model. Interestingly, authors proposed in this work a time-lapse quantitative biodistribution approach to follow mpEVs transport through nasal and intra-cranial tissues until they reached GBM tumor tissue; this was possible by combining *in vivo* and *ex-vivo* imaging techniques using ICG dye properties [242].

5. Challenges and future perspectives of EVs in clinics

EVs represent promising tools in hand in clinics serving as sources of diagnostic biomarkers as well as therapeutic means for innovative

strategies in cancer treatment such as in GBM. Experimental evidence gathered so far is exciting, however its translation into the clinical practice is challenging and still far from being achieved. The main challenges are represented by isolation/purification methods which allows a proper characterization of the material obtained from biological fluids. Indeed, lack of standardized protocols for the isolation, characterization, and validation of EVs hinders their reliability as sources of diagnostic biomarkers.

Furthermore, existing techniques for EV characterization are time-consuming, labor-intensive, and require specialized equipment and expertise. Furthermore, what makes the picture arduous is the biological complexity of the system being EVs subpopulations highly heterogeneous in their composition. Understanding this complexity and its implications for clinical applications is essential.

All these aspects lead to a wide variability and limited reproducibility of the results across different studies, underlying the urgency of validation through different methods of a single or a panel of EVs-associated biomarkers, to make EVs an increasingly reliable diagnostic tool [243]. Regarding the potential that EVs have shown as therapeutic tools for cancer treatment, including GBM, many advantages have been evaluated, such as high biocompatibility, low immunogenicity, poor toxicity, high targetability, and natural disposition; however, several issues are still open and represent unresolved challenges including loading efficiency, poor scalability, off-target effects, low production yields, and importantly integrity and stability. Finally, safety issue is another critical point since to date only a few works have employed EVs in *in vivo* systems. Further preclinical and clinical studies are needed to assess the long-term effects and potential adverse reactions associated with EV-based interventions.

6. Conclusions

Studying the functions, structure, and cargo components of EVs has gained significant attention as potential tools for early cancer diagnosis and therapeutic intervention. In particular, in the era of precision medicine, the use of EVs in GBM could represent a powerful tool capable of significantly advancing the clinical management of this dismal disease from a diagnostic, follow-up and therapeutic point of view. Indeed, while we are witnessing of a notable progress in exploring the use of EVs in GBM, translating these findings into clinical applications is still a significant challenge. It is therefore realistic to state that utilizing patient-derived EVs for diagnostic and therapeutic purposes will require intense methodologies optimization able to overcome challenges before these applications can be widely adopted in clinical settings.

In conclusion, while the use of EVs in GBM holds great promise, there's urgency to address all the technical and clinical issues for successful translation into routine medical practice. Fostering collaboration and encouraging a multidisciplinary approach is imperative to accelerate research progress, and potentially realize the benefits of EVs-based diagnostic and therapeutic strategies for GBM patients in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

Acknowledgment

This work was supported by Fondazione-AIRC: GS [IG 2021 id 25696].

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