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Extracellular Vesicles in the Glioblastoma Microenvironment: A Diagnostic and Therapeutic Perspective

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Abstract

Glioblastoma (GBM), is the most malignant form of gliomas and the most common and lethal primary brain tumor in adults. Conventional cancer treatments have limited to no efficacy on GBM. GBM cells respond and adapt to the surrounding brain parenchyma known as tumor microenvironment (TME) to promote tumor preservation. Among specific TME, there are 3 of particular interest for GBM biology: the perivascular niche, the subventricular zone neurogenic niche, and the immune microenvironment. GBM cells and TME cells present a reciprocal feedback which results in tumor maintenance. One way that these cells can communicate is through extracellular vesicles. These vesicles include exosomes and microvesicles that have the ability to carry both cancerous and non-cancerous cargo, such as miRNA, RNA, proteins, lipids, and DNA. In this review we will discuss the booming topic that is extracellular vesicles, and how they have the novelty to be a diagnostic and targetable vehicle for GBM.

Keywords

glioblastoma multiforme; tumor microenvironment; perivascular niche; subventricular zone/ neurogenic niche; exosomes; microvesicles

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Author Contributions

MNR, LAW, and HGC were responsible for the conceptualization, literature review, figure production, and writing of the manuscript. ESN and NZ were responsible for writing and proofreading the manuscript. Both MNR and LAW contributed equally to this work and have the right to list their name first in their CV. All authors contributed to and approved the final version of this manuscript.

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Competing Interests Statement

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1. Introduction

Glioblastoma multiforme, or GBM, is the most malignant form of gliomas and is considered the most common and lethal primary brain tumor in adults. Despite current standard of care, the median survival of GBM patients remains at 14–16 months after diagnosis, 70% of patients will present disease progression after one year of diagnosis and less than 5% of patients survive past five years (Davis, 2016). Under current brain tumor classification, GBM arise de novo (previously called primary GBM) and present a wild type form of IDH1 gene. Grade 4, IDH1 mutant tumors, which can progress from lower grade gliomas (previously known as secondary GBM) are currently known as Grade 4 astrocytoma (Louis et al., 2021). The median age of diagnosis is 65 years old, with an incidence of 3 cases in 100,000 people with a slight increased incidence in men than women (Ostrom et al., 2020). Patients with suspected high-grade glioma are initially subject to a physical and clinical evaluation, followed by a contrasted MRI. Definite diagnosis of GBM is done by histological analysis of a tissue biopsy or tumor resection. Current glioma classification considers histopathology findings and key molecular tests (Ostrom et al., 2020). The current standard of care for GBM was largely established almost 2 decades ago, with little modifications (Stupp et al. 2005). This protocol includes maximal safe surgical resection followed by concurrent postoperative radiation therapy with oral alkylating chemotherapy agent, Temozolomide (TMZ). This treatment protocol has shown to extend median patient survival from 12.1 months to 14.6. However, this multidisciplinary approach is not curative for GBM patients (Louis et al., 2021; Stupp et al., 2005).

Histologically, GBM presents as a diffuse glioma (D'Alessio et al., 2019) with microvascular proliferation and pseudopalisading necrosis as pathognomonic histological features. Additional aspects can be observed, such as hypercellularity, nuclear atypia (D'Alessio et al., 2019), and multinucleated giant cells (Jaiswal et al., 2012). Histological analyses remain an important and regularly used tool for clinical diagnosis. Moreover, technological advancements and discoveries particularly in "-omics" related fields continually improve scientific understanding of these tumors at a molecular level.

While GBM is considered a singular diagnosis, there is considerable intertumoral heterogeneity as observed in transcriptome, mutation, and copy number variations (Brennan et al., 2013; Verhaak et al., 2010). Four GBM subtypes were identified from these analyses: Classical, mesenchymal, proneural, and proliferative. However, the impact of this classification on patient survival and treatment response has been marginal and continues to be evaluated (Wang et al., 2020). Nevertheless, the concept of additional GBM molecular stratification continues to be enhanced as scientists pursue more effective classification methods beyond DNAm (DNA methylation) and gene-expression based classifiers only (Ensenyat-Mendez et al., 2021). Collectively, this further categorization is critical for patient prognosis as these different molecular subtypes could give rise to subtype-specific treatments that address these molecular variations, potentially increasing treatment efficacy for patients. Furthermore, single cell sequencing technology has allowed to demonstrate GBM heterogeneity is also present intratumorally (Patel et al., 2014). This characteristic functions as a major determining factor of treatment efficacy, potential recurrence, and

overall prognosis (Bedard et al., 2013; Patel et al., 2014). The prevalent intra- and inter-tumoral heterogeneity in GBM calls for more studies focused on its regulatory mechanisms.

The source of intratumoral heterogeneity hints at the idea of a common cellular source with pluripotent capabilities. Stem cells in cancer were initially described in liquid malignancies and eventually in GBM (Gimple et al., 2019; Singh et al., 2004). Glioblastoma stem cells (GSC) are believed to be major contributors to tumor growth, recurrence, and heterogeneity (Gimple et al., 2019). These are cells with slower proliferation rate (quiescent) and the ability to self-renew, give rise to differentiated progeny, and generate a tumor with GBM features, upon secondary transplantation. GSCs are strongly influenced by the surrounding environment, including cellular components, oxygen tension, genetic factors, and soluble proteins (Lathia et al., 2015; Mohyeldin et al., 2010). The elimination of GSCs has been the focus of multiple research studies with unsatisfactory results. GSC display resistance towards radiotherapy (Bao et al., 2006) as well as TMZ chemotherapy (Chen et al., 2012; Liu et al., 2006).

2. Glioblastoma Multiforme tumor microenvironment

The tumor microenvironment (TME) is the ecosystem of cells and extracellular components surrounding tumor cells. The cell populations within this environment coordinate to adapt in ways that collectively favor and support survival of cancer cells as well as facilitating local invasion, making the TME highly dynamic (Anderson and Simon, 2020). TMEs generally consist of tumor cells, stroma, blood vessels and vascular components, and infiltrating inflammatory cells (Whiteside, 2008). The GBM TME includes these same components while displaying particular heterogeneity. GSC and differentiated GBM cells (DGCs) are the major proliferating tumor cell populations. The non-tumor cells that are typically present include endothelial and vascular pericytes (Charles and Holland, 2010) (Anderson and Simon 2020). GBMs also have an immunosuppressive TME. In this environment, immune cells that would carry out tumor-suppressing activities transition towards a state promoting inflammation and/or tumor escape. These altered immune cells include innate and recruited/infiltrative cells such as microglia, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and glioblastoma associated myeloid cells (GAMs) (Darmanis et al., 2017; Gabrusiewicz et al., 2016; Shi et al., 2015). This environment is complex as the tumor mass itself can actively change the TME, while the TME also affects the growth of the tumor. The interactions taking place between the neighboring cancer and non-transformed cells make the TME a key component in tumor progression (Balkwill et al., 2012). The diffusion of cytokines, chemokine, growth factors, and matrix remodeling enzymes drives this bidirectional intercellular communication shared between the tumor cells and their TME (Balkwill et al., 2012) as the dynamic activities of these molecules trigger responsive alterations to local/surrounding tissue.

In the brain, some areas present tumor promoting conditions as they interact with GBM tumors. Of particular interest in this review are the Subventricular Zone (SVZ) neurogenic niche in the lateral wall of the lateral ventricles (LV), the immune microenvironment, and the Perivascular Niche (PVN).

2.1 The neurogenic niche

Postnatally, in mammalian brains, the largest region that maintains its capacity of producing neural stem cells (NSCs) is the SVZ (Alvarez-Buylla et al., 1998; Luskin, 1993; Reznikov, 1991; Sanai et al., 2004). The SVZ anatomy of adult humans consists of 4 layers. The first being comprised of an ependymal cell monolayer facing towards the lateral ventricle cavity. Behind the ependymal layer, there is a hypocellular gap, consisting of intertwined processes of Glial Fibrillary Acidic Protein (GFAP)-positive astrocytes. The third layer contains an astrocytic ribbon along (Quiñones-Hinojosa et al., 2006; Sanai et al., 2004)

GBM patients with tumors in direct contact with the LVs have worse prognosis with lower survival rates than GBMs not contacting the lateral ventricles (Chaichana et al., 2008; Mistry et al., 2017; Mistry et al., 2019). Additionally, GBM in contact with the lateral ventricles show higher incidence of distal recurrence, compared to GBM distant from lateral ventricles vicinity (Lim et al., 2007). The mechanisms behind this increased malignancy of GBM tumors proximal to the lateral ventricles are not well understood. Interactions between SVZ-NSCs, GBM cells, and the lateral ventricles alter this specific region in ways that influence tumor progression. In animal models of LV-proximal GBM, tumor proximity causes a decrease in NSC proliferation and decreases SVZ-derived neuroblasts migration. This animal model replicates important clinical observations present in patients, like lowered survival and increased tumor cell proliferation (Ripari et al., 2021). In bulk tumor samples from patients, LV-proximal GBM show similar transcriptome profiles, when compared to LV-distal samples (Mistry et al., 2019; Steed et al., 2016; Steed et al., 2020). However, this phenomenon should be studied at a single cell level due to the intratumoral heterogeneity mentioned above.

2.2 Immune microenvironment

A collection of non-neoplastic immune cells, such as macrophages, microglia, and reactive astrocytes also take residency in the TME forming an immune microenvironment inside and around the tumor (Chen and Hambardzumyan, 2018; Henrik Heiland et al., 2019). TAMs originate from microglia found in the brain and are considered the dominant infiltrating immune population as they make up approximately 30–40% of the cell population in GBM (Engler et al., 2012). These cells infiltrate the tumor guided by chemoattractants, such as osteopontin (OPN) and glial cell-derived neurotrophic factor (GDNF), released into the extracellular environment by tumor cells (Andersen et al., 2021).

The amount of tumor-associated microglia and TAM is positively associated with immunoregulation in glioma, giving this recruitment of cells clinical relevance(Chen et al., 2020; Zhang et al., 2021a). The impact of GBM on immune cells in the brain induces a strong inhibition of anti-tumor T cell response and bone marrow entrapment of T cells (Chongsathidkiet et al., 2018). Additionally, tumor cells release ligands like PD-L1 which upon binding to the PD1 receptor induces an immune evasion response. Importantly, tumor-infiltrating lymphocytes show a higher expression of checkpoint molecules like PD-1, LAG3 and TIM-3 which impairs their activity against tumor cells (Davidson et al., 2019; Pombo Antunes et al., 2020). Overall, GBM cells and immune cells present constant intercommunication that results in a defective anti-tumor immune response.

2.3 Perivascular niche

One of the GBM TME areas particularly enriched for GSCs is the regions surrounding small blood vessels and capillaries, known as the PVN. (Calabrese et al., 2007; Charles et al., 2010; Hambardzumyan et al., 2008). In the PVN, GSC are maintained by signals from endothelial cells like Notch, OPN, and nitric oxide (Calabrese et al., 2007; Charles et al., 2010; Stroeher et al., 1988). Additionally, GBM cells utilize blood vessels (and myelin tracts) as roads to invade the brain parenchyma (Farin et al., 2006; Riquelme et al., 2008; Watkins et al., 2014; Winkler et al., 2009). The interaction of GSCs with the PVN microenvironment contributes to tumor expansion cellular heterogeneity. There are endothelial and stromal cells, such as fibroblasts and pericytes, that make up most of this niche and drive the progression of GBM (Charles and Holland, 2010; Charles et al., 2012). Pericytes surround, stabilize, and help maintain the integrity of the newly developed vasculature walls (Gerhardt and Betsholtz, 2003). Recruitment of these cells is driven by overexpression of Platelet Derived Growth Factor Receptor Beta/Platelet Derived Growth Factor B (PDGFRβ/PDGFB) to newly developing vessels (Bergers and Song, 2005; Dunn et al., 2000), and contributes to stabilization of tumor vessels in many different types of cancers (Guo et al., 2003; Rajantie et al., 2004; Song et al., 2005). In addition to the major cell types found in the PVN, one can also find immune cells including lymphocytes, macrophages, microglia, astrocytes (Charles and Holland, 2010). There are additional similar signaling pathways and genes upregulated in the PVN that are implicated in cancers, such as O^6-methylguanine-DNA methyltransferase (MGMT), Epidermal Growth Factor Receptor (EGFR), and PI3k-Akt and Ras/MAPK signaling (Ngo and Harley, 2019).

3. Characterization of extracellular vesicles

Intercellular communication in the GBM TME includes soluble factors diffusing through the extracellular matrix, direct cell-cell contact, like Notch activation, and signaling molecules encapsulated in extracellular vesicles (EVs)(Fig. 2). EVs are a heterogenous group of cell-derived membranous structures that provide a mechanism for intercellular communication, allowing for cells to exchange proteins, lipids, RNA, and other genetic material (van Niel et al., 2018). The term EVs encompasses a variety of different membrane secreted vesicles, which makes characterization of these vesicles an ongoing field of study. Due to the similar morphology and overlapping size of different EV, complete characterization and distinction remain onerous. Based on what has been discovered, the two defined categories of EVs are exosomes and microvesicles.

Exosomes are typically 30–100nm in diameter (Johnstone et al., 1987), and form due to an invagination of the endosomal membrane as intraluminal vesicles (ILVs), which are then secreted during fusion of multivesicular bodies (MVBs) to the cell surface (Harding et al., 1984; van Niel et al., 2018). There are two known machineries involved in the biogenesis of exosomes: endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent. The ESCRT machinery pathway modulates the production of exosomes by regulating the formation of ILVs and MVBs (Hurley, 2008; van Niel et al., 2018). This pathway begins with ESCRT0 and ESCRTI gathering ubiquitylated cargoes from MVBs, which then recruits the ESCRTIII subunit, with the help of ESCRTII, to cause

exosome budding (van Niel et al., 2018). The ESCRT-independent pathway operates through the generation of ceramide to impose negative curvature on the membranes to help with the formation of exosomes, or by the metabolism of ceramide to activate G-protein-coupled sphingosine 1-phosphate receptor, an important mechanism for sorting exosomal cargo into ILVs (Goñi and Alonso, 2009; Kajimoto et al., 2013; Trajkovic et al., 2008). In addition to the ceramide driven ESCRT-independent mechanisms, proteins in the tetraspanin family are also involved in endosomal sorting, such as CD63, CD81, CD9, ALIX, and TSG101 which are enriched on the surface of exosomes and used as characteristic markers (Buschow et al., 2009; Chairoungdua et al., 2010; van Niel et al., 2011) (Fig. 2). The release of exosomes is mediated by multiple protein families. For example, Ras-related proteins (RAB11, RAB35, RAB27) help to promote secretion, along with SNARE proteins (SNAP25, SNAP23) that help mediate membrane fusion and cell navigation (Colombo et al., 2014; Zylbersztejn and Galli, 2011).

The second characterized group of EVs are microvesicles, which are typically 50–1000nm in diameter (van Niel et al., 2018). They form via an outward budding of the plasma membrane, resulting in a release of these vesicles into extracellular space (Tricarico et al., 2017). The biogenesis of microvesicles requires changes in lipid and protein composition within the plasma membrane, although specific mechanisms are still being investigated (Theos et al., 2006). Lipids such as cholesterol (Del Conde et al., 2005) and the activity of RHO family of GTPases and the RHO-associated protein 30kinase (ROCK) are involved in the formation of microvesicles in certain tumor cells (Li et al., 2012). Additionally, the Ca^{2+} levels and the enzymatic machineries driven by Ca^{2+} promote physical tension on the plasma membrane, which helps to restructure the actin cytoskeleton and favor budding of microvesicles (Al-Nedawi et al., 2008; Piccin et al., 2007). Similar to the mechanisms involved in retroviral budding, microvesicle-targeted cargo is regulated through their affinity to lipid rafts or their anchoring to plasma membrane lipids (Shen et al., 2011; Yang and Gould, 2013). The budding of microvesicles from the plasma membrane is mediated by ADP-ribosylation factor 6 (ARF6) and other components of the ESCRT pathway (Colombo et al., 2014). In comparison to the known exosome markers, the known markers for microvesicles also include heat shock protein (HSP) 90B1, glycoprotein 1b, actinin-4, mitofilin, and myosin light chain (Bruschi et al., 2019; Haraszti et al., 2016; Kowal et al., 2016; Zhang et al., 2018) (Fig. 2).

3.1 Current extracellular vesicle isolation methods

EV extraction can be done from a variety of different samples, such as human brain tissue, cerebrospinal fluid (CSF), blood, as well as from mouse tissue and primary and secondary cell culture (Muraoka et al., 2020; Théry et al., 2018). Due to not having a complete understanding of the characterization of these EVs, the extraction processes can be variable. The proper extraction methods for the different kinds of EVs are still debatable, causing there to be a myriad of protocols available. There is no current gold standard for EV isolation, especially one that is applicable to extraction from all biofluids. In a recently updated guideline published in 2018 titled Minimal Information for Studies of Extracellular Vesicles (MISEV), the authors describe the different methods of separating EVs and create guidelines for verifying that the isolated sample effectively yields EVs (Théry et al., 2018).

EV separation from frozen unfixed human and mouse brain tissue has been done successfully. The methods begin with digestion of the brain tissue, followed by differential centrifugation, and completed with either a sucrose gradient ultracentrifugation (SG-UC) or size exclusion chromatography (qEV) (Muraoka et al., 2020). When using both SG-UC and qEV, although qEV yielded a higher EV particle number compared to SG-UC, both methods showed the EVs to be enriched in the necessary EV identification markers, such as CD9, CD81, annexins, and other specific lysosomal markers (Muraoka et al., 2020). Additionally, EVs can also be isolated from cells grown in vitro, using methods such as differential centrifugation and ultracentrifugation (Mathivanan et al., 2010b), precipitation kits (ExoQuick) (Kaur et al., 2014) or the use of total exosome isolation reagent (Wen et al., 2020). Interestingly, there is also an EV capture method that uses a synthetic peptide (Vn96) that has a high binding affinity to heat shock proteins, that proved to be superior to ultracentrifugation (Ghosh et al., 2014). This method captures EVs from small samples, and is available mainly for cells in culture, but can also be applied to biofluids such as plasma and urine.

Isolating EVs from fixed frozen brain tissues or cells grown in vitro is helpful for identifying potential biomarkers, but it is the use of biofluids which takes extraction of EVs from the bench to the clinic. There are many available biofluids to separate EVs from, such as plasma, serum, cerebrospinal fluid, and saliva. In blood, there is the choice to isolate sera or plasma. EVs are more easily recovered from and are more abundant in sera than plasma (George et al., 1982). Additionally, a study published in 2012, analyzing micro-RNA expression in early non-small cell lung cancer, found that expression levels in serum did not correlate with the levels in plasma (Heegaard et al., 2012). The available methods for isolating EVs from plasma are size exclusion chromatography, ultracentrifugation, and precipitation kits (ExoQuick and ExoQuick ULTRA) (Ter-Ovanesyan et al., 2021). These methods are still being optimized and compared for contamination level, relative EV recovery, and known surface markers such as CD81, CD63, and CD9 (Ter-Ovanesyan et al., 2021). Overall, additional studies need to be run in order to identify the most reliable option for serum and plasma EV isolation. Another available biofluid that contains EVs is CSF, although it has been reported to be difficult to retrieve a large amount from realistic samples of CSF (Street et al., 2012). The available methods for isolation of EVs from CSF range from differential centrifugation and affinity capture (MagCapture) (Muraoka et al., 2020), to precipitation kits (ExoQuick and ExoQuick ULTRA), qEV and ultracentrifugation (Ter-Ovanesyan et al., 2021). Saliva, a more readily available biofluid, is also an explored source to isolate EVs. In this case, differential centrifugation, ultracentrifugation (Lässer et al., 2011; Sharma et al., 2011) and gel filtration (Ogawa et al., 2008) are the few studied methods for saliva EVs. Overall, over the past decade, the methods for separation of EVs have continued to evolve which is why it is imperative to establish reliable and non-variable methods for this field of study.

4. Extracellular vesicle role in glioblastoma multiforme

EVs derived from gliomas or non-glioma cells in the tumor microenvironment are involved in tumor cell proliferation, invasion, malignancy, and drug resistance (Balakrishnan et al., 2020; Matarredona and Pastor, 2019; Mathieu et al., 2019; Xia et al., 2019). Cancer cells

are shown to release higher amounts of EVs compared to non-malignant cells, and these cancer EVs are what help communicate with other nearby cells, leading to promotion of tumorigenesis (Bebelman et al., 2018). Additionally, cancer EVs alter the behavior of the local and recruited pericytes or other cells, which results in the generation of a tumor-promoting niche supporting tumor angiogenesis, immunosuppression, and the acquisition of malignant traits by cancer cells (Bebelman et al., 2018).

The development of a perfect method to purify EVs may still be in progress, but there have been explorations in extracting RNA from different biofluid-derived EVs. For example, blood plasma is the most used source of EV-RNAs, as it mainly contains EVs present in circulating blood, compared to using blood serum that contains EVs released by platelets (Antwi-Baffour et al., 2015; Mateescu et al., 2017). Studies have shown EV-contained miRNA 21 (miR-21) and miRNA 128 (miR-128) were upregulated in the blood of GBM patients (Holdhoff et al., 2013; Roth et al., 2011). Furthermore, when comparing levels of miR-21 expression between patients with and without GBM, the levels of miR-21 are significantly greater in microvesicles originating from the CSF of patients with GBM (Akers et al., 2013). The actual process of RNA sorting into EVs of specific cell types is unknown but thought to be specific to parent cell and location of formation of EVs. Most EV isolation methods are not able to distinguish between different vesicle subpopulations (exosomes vs microvesicles), and the exact subpopulations relevant to a particular disease state, making sorting of RNA difficult to detect in heterogeneous EV mixtures (Mateescu et al., 2017). Additionally, the amount of sample available can act as a limiting factor, especially when trying to isolate such a small amount of EVs, and subsequently, a small amount of RNA. There are, however, ways to distinguish the origination of vesicle based on the RNA cargo contained or released from a group of EVs.

In addition to obtaining RNA and DNA from EVs, researchers have been able to identify protein content in EVs. In a recent 2021 publication, Greco et al compare serum-derived EV protein profiles against murine CSF and serum, and conclude there to be significant differences in protein levels contained in EVs compared to these two biofluids during GBM progression (Greco et al., 2021). Additionally, proteins such as GFAP, Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), Chitinase-3-Like Protein (CHI3L1 or YKL-40), and Matrix Metalloproteinase 9 (MMP9) (Redzic et al., 2014), have been identified as potential EV biomarkers in GBM.

EVs contain abundant proteins and RNAs that can serve as biomarkers for cancer. There have been several potential cancer markers identified from different biofluids (Li et al., 2017). As mentioned, GBM has shown to have a complicated genetic profile as the disease is considered to be pathologically and clinically heterogeneous (Bedard et al., 2013). The involvement of EV in GBM biology and the increasing availability of technologies to study them allows scientists to explore the roles of EV content in tumor progression, biomarker research, and therapeutic approaches. Here, we will take the time to delve into the three niches described above (SVZ, PVN, and the immune microenvironment), their specific EV cargo, and the impact this interaction can have on GBM diagnosis and prognosis.

4.1 Neurogenic niche cell specific extracellular vesicle cargo

GSCs, neurons, and glia form and release EVs within the neurogenic niche (Losurdo and Grilli, 2020). With EVs being recognized for their contribution to intercellular gene regulation, it is no surprise that they play key roles in the maintenance and homeostasis of the neurogenic niche and its interaction with GBM.

In some cases, the EVs released by GSCs help establish a fundamental crosstalk with other local GSCs. miRNA-21a has been identified in NSC-EV cargo through RNA sequencing and is shown to increase NSC proliferation via targeting the genes SOX2 and Stat3 (Ma et al., 2019a) , both of which contribute to GBM malignancy and are upregulated in GBM (Li et al., 2019). NPC-EVs also contain growth-factor-associated proteins, such as EGF-like domain and the EGF-like calcium-binding domain, which also promote GSC proliferation but instead by means of ERK pathways downstream (Ma et al., 2019b). Along with those that moderate stem cell quiescence/proliferation ratio, other molecules with roles in regulating adult neurogenesis and NSC fate have been identified in the cargo of NSC and NPC-EVs (Losurdo and Grilli, 2020). This would include miR-9 (Xia et al., 2019; Zhao et al., 2009), miR-let7b (Ma et al., 2019a; Morton et al., 2018; Zhao et al., 2010), miR-124, and miR-137 (Bielefeld et al., 2017).

Aside from initiating positive and negative feedback loops amongst themselves (NSCs), many of the miRNAs being carried and released by GSC-derived EVs appear to have immunological relevance as they show to selectively target microglia. For instance, miR-9, miR-let-7, miR-26a, miR-181c have been identified in GSC-EVs and are known to be associated with microglia physiology and general morphology (Kumar et al., 2015; Lehmann et al., 2012; Yao et al., 2014; Zhang et al., 2015). In some studies, SVZ NSC-EVs were shown to function as microglia morphogens as they were observed to activated immune/inflammatory response-related transcriptional programs (Morton et al. 2018). These NSC-EVs show to bridge communication between the immune microenvironment and the neurogenic niche as said EVs have displayed their potential to increase the number of CD11b+ microglia and increase their cytokine release in the SVZ (Morton et al., 2018). What makes this type of immune-associated interaction even more interesting, this communication still takes place between host microglia and grafted NPCs (Cossetti et al., 2014; Matarredona et al., 2018; Pluchino and Cossetti, 2013). Other studies have noted an upregulated expression of CD11b in microglia to be associated with activation (Hoek et al., 2000; Kierdorf and Prinz, 2013).

However, this EV-based cross talk stemming out of the neurogenic niche proves to be bilateral. Specifically, EVs generated by non-GSCs are capable of altering cellular mechanisms of neurogenic niche components, especially in the context/framework of GBM. To regulate its TME, GBM cells can recruit and alter the phenotype of non-tumor cells (Wang et al., 2019). It’s also been observed that NSCs can advance tumorigenesis by migrating towards gliomas to then disperse throughout the tumor bed (Aboody et al., 2000). EVs have the potential to contribute to diverse processes in cell-cell communication. The specific mechanisms affected by EVs depend upon the cellular microenvironment as this determines the contents packaged into EV (Bahram Sangani et al., 2021; Cossetti et al., 2014). In the case of NSC cultures treated with glioblastoma-derived EVs, the cells appeared

to increase in proliferation and migration rate resembling that of a transformed cell. In other words, it was confirmed that GBM cells could carry over biological information to local NSCs in a way that transformed them into becoming cancerous (Wang et al., 2019). Considering that recurrent GBMs are often found in white matter bordering regions like the SVZ and the poor prognosis of SVZ-contacting GBM patients (compared to non-contacting SVZ GBM) (Ellingson et al., 2013), EVs may provide an explanation or may even function as an agent that prompts this phenomenon.

4.2 Immune microenvironment cell specific extracellular vesicle cargo

Microglia and astrocytes are two important components of an intracranial tumor immune microenvironment, where both display plasticity in their nature/behavior to either induce or hinder neurogenic processes, eliciting appropriate responses to changes in the neurogenic niche. Microglia activity can tip the scale of adult neurogenesis by either inducing or hindering the proliferation of NSCs, as well as the differentiation and survival of adult-borne neurons (Losurdo and Grilli 2020). Cytokines generated and released by microglia have a significant impact on adult neurogenesis given their ability to prompt different inflammatory processes in the brain. EVs released by M1-phase, or active microglia have been found to carry cytokines as well, such as interleukin-6 (IL-6), that promote NSC proliferation as well as neuronal maturation (Bowen et al., 2011). Similarly, reactive astrocytes (or RAs) also play a role in controlling neurogenesis bidirectionally. EVs released by these astrocytes contain enzymes such as EAAT-1 (Espósito et al., 2005; Ge et al., 2006) and NTPDases (Gampe et al., 2015) which can increase GSC differentiation and decrease NSC proliferation respectively (Losurdo and Grilli, 2020). Astrocyte-derived EVs were also found to carry neuroglobin, which functions as a neuroprotectant while simultaneously carrying out increased GSC proliferation associated with Wnt signaling in numerous brain injury models (Yu et al., 2018b).

The reciprocal aspect of this relationship shows EVs generated and released by neighboring GBM cells can manipulate these processes and their resulting products to favor or hinder GSC-related mechanisms maintaining the TME. Similar to what was described with gliomas cells inducing NSCs towards a tumor-promoting phenotype, glioma cells show a similar ability to induce the transition of an astrocyte in an active-phase or reactive astrocyte (Yu et al., 2018a). Consequentially, this transformed type of astrocyte has been seen to carry and release O6-alkylguanine DNA alkyltransferase (AGT) to other local glioma cells (Yu et al., 2018a). This cargo holds clinical relevance as it is associated with TMZ resistance in tumor treatments like that for GBM (Fig. 1).

4.3 Perivascular niche cell specific extracellular vesicle cargo

Due to its proximity to blood vessels, the PVN is characterized by being involved in angiogenesis, but also notably responsible for tumor invasion, NSC survival, and drug resistance. In vitro, genes related to angiogenesis, such as HAS1, VEGF, PDGFR, EGFR, MMP9, TNC, were upregulated in GBM (Ngo and Harley, 2019). Most of these observed upregulated genes are members of signaling pathways that are known to be altered in GBM. We know that proteins from a few of the markers listed above can be successfully isolated from EVs, and therefore used as potential specific biomarkers for the PVN in GBM. Severity

of the tumor progression can be measured using these biomarkers extracted from EVs. There are many different cell types that interact in the PVN, and therefore provide several potential cell specific EV markers. For example, GSCs are differentiated into pericytes by TGF-b (Cheng et al., 2013), an exosomal surface marker (Shelke et al., 2019), and therefore a possible biomarker of PVN derived EVs. Furthermore, GSCs in the PVN recruit TAMs that promote tumor growth, while also inducing overexpression of MMP9 (Ye et al., 2012; Zhou et al., 2015), making this protein a potential candidate biomarker in the PVN. There also have been many other pathways that have been identified to be crucial in GBM-PVN interactions and serve as prospective biomarkers and targetable axes for therapy. These include Wnt5 (Hu et al., 2016), Notch (Zhu et al., 2011), integrin a6 (Lathia et al., 2010), angiopoietin 2 (Bentolila et al., 2016), L1CAM (Burgett et al., 2016), SEMA3C (Man et al., 2014), and bradykinin (Montana and Sontheimer, 2011), all of which are involved in GSC survival, progression, and angiogenesis. To date, there are no miRNA markers specific to the GBM-PVN model (Fig. 1).

5. Translational Uses of EVs

As previously discussed, EVs contain many proteins and types of RNAs that can be isolated and traced to specific brain regions. Both exosomes and microvesicles have specific surface markers, and therefore allow EVs to be purified from many different biological samples by checking for the presence of these markers. Moreover, we also discussed certain miRNAs (Holdhoff et al., 2013; Roth et al., 2011) and proteins (Redzic et al., 2014) that are being explored as possible biomarkers for GBM. Different cellular components released by tumor cells or antigen presenting cells (dendritic cells, macrophages, B cells) can be efficiently packaged into exosomes and serve as cargo transporters in cancers (Tran et al., 2015). By combining what is known about EVs and GBM, there is potential to use GBM-EVs and the cells involved as both a diagnostic and therapeutic tool.

For diagnostic purposes, EV cargo can act as the perfect biomarkers for GBM. Previous studies have shown that cancer cell derived EVs are highly enriched in proangiogenic factors miR-9 (Zhuang et al., 2012) and miR210 (Tadokoro et al., 2013), signaling factors involved in cell invasion, such as IL-6 and VEGF (Skog et al., 2008), and promoters of tumor progression such as neutral sphingomyelinase 2 (nSMase 2) (Kosaka et al., 2013). Additionally, differing expression levels of circulating miR-146b, miR-221, miR-let7a, miR-155, miR-17–5p, miR-27a and miR-106a in serum and plasma in small cell lung cancer correlated with different patient mortality stages (Heegaard et al., 2012). In GBM, miR-21 and miR-128 were upregulated in the blood and CSF in microvesicles of GBM patients (Akers et al., 2013; Holdhoff et al., 2013; Roth et al., 2011). Furthermore, proteins such as GFAP, VEGF, bFGF, CHI3L1, MMP9 (Redzic et al., 2014), have been identified as potential biomarkers in GBM. In a proteomic study of serum derived EVs, Greco et al., identified 9 proteins that were present in all serum EV samples (Greco et al., 2021), making these proteins additional potential biomarkers in this specific biofluid. Using EVs and their cargo as a diagnostic tool for GBM is the first step in gaining a better characterization of these highly heterogenous tumors. As discussed above, there are many already identified potential biomarkers for GBM, but much more work needs to be done in this elusive field. Together,

the known biomarkers that are upregulated in GBM, need to be investigated further in the context of applying them as GBM-EV biomarkers (Table 1).

EVs could also act as delivery vehicles for tumors. Drug resistance has been a large obstacle to evade when attempting to treat cancers, leaving many tumor cells to have a low drug response rate. Since EVs serve as intercellular communicators (Mathivanan et al., 2010a), they are able to interact with membranes of other cells and deliver cargo (Théry et al., 2006; van Niel et al., 2018). A previous study looking at multiple drug resistance (MDR) in cancer has shown that exosomes released by macrophages carrying paclitaxel (PTX) have a higher cytotoxicity to drug resistant cells (Kim et al., 2016). Additionally, breast cancer cell derived EVs can transfer resistance of docetaxel, an anti-cancer chemotherapy drug, to cells that are sensitive to the drug (Lv et al., 2014). In non-small cell lung carcinoma cells, the transfer of the pro-survival Akt/mTOR complex through EV cargo leads to resistance to gefitinib (Choi et al., 2014), a typical drug used to treat non-small cell lung cancer. In regard to glioblastoma, reactive astrocyte exosomes can deliver AGT to glioma cells, resulting in TMZ resistance in cancer cells (Yu et al., 2018a). An early study conducted in 2011 used exosome mediated delivery of Lamp2b, and exosomal membrane protein, from engineered dendritic cells in mice to silence genes related to Alzheimer's Disease (Alvarez-Erviti et al., 2011). Additionally, researchers found a crosstalk between cardiac fibroblasts that secrete miR-21 from their exosomes to cardiomyocytes, inducing hypertrophy (Bang et al., 2014). Mechanistic studies have shown that activation of the PI3K-Akt signaling pathway is how glioblastoma cell-derived EVs have their effect on promoting tumorigenesis on recipient NPCs, but when inhibiting this pathway, the effect of GSC-EVs on target cells is reversed (Pan et al., 2022). In ovarian serious cystadenocarcinoma, normal and overexpression of exosome protein miR-940 inhibits proliferation and migration, triggers cell cycle arrest, and reduces downstream signaling of cancer promoting pathways such as PI3K-Akt and FAK (Rashed et al., 2017). The PTEN/AKT cancer signaling pathway can be targeted by MSC-EV delivery of miR-144, in order to alleviate cell apoptotic injury in hypoxic conditions (Wen et al., 2020).

Moreover, EVs derived from the tumor microenvironment are involved in tumor cell proliferation, invasion, and malignancy of the tumor (Mathieu et al., 2019; Xia et al., 2019). Due to the numerous cell types in the tumor microenvironment, crosstalk between cells is common, and even promoted when in the presence of EVs (Mathivanan et al., 2010a). Mesenchymal stem cells (MSCs) are one source of EVs (Pascucci et al., 2014) that were previously discussed as an avenue for drug therapeutics, but there are other cell types that produce EVs. T cell derived EVs expressing CD47, were shown to interact with endothelial cells and alter gene expression of endothelial genes, which in turn affects cell proliferation and other physiological processes (Kaur et al., 2014). MSC-derived microvesicles that are carrying PTX show a strong anti-proliferative activity on human pancreatic cancer cell lines (Pascucci et al., 2014). More recently, bone marrow MSC exosomes show improved tumor targeting and accumulation of drug at the site of the tumor in pancreatic cancer cells (Zhou et al., 2021). Additionally, MSCs that were engineered to express miR-29a-3p successfully delivered this miRNA to cells, causing tumor suppressive effects, such as inhibition of migration and alternative angiogenesis in gliomas (Zhang et al., 2021b). These results are promising because it shows the ability of MSCs to package and deliver active drugs through

their microvesicle and exosomal cargo, opening a new door for using MSC-EVs as a potential trojan horse in drug delivery. In brain tumors, the concept of targeting glioblastoma progression with engineered MSCs and using EVs as drug delivery vehicles still needs to be explored despite promising results when examining other cancers.

In addition to using EVs as a therapeutic target, researchers have become more interested in targeting the EV formation pathway with the goal of reducing EV formation in cancer cells. For instance, silencing and inhibiting CD9 to evaluate the production and release of EV resulted in the triggering of a compensatory mechanism to maintain EV production (Suárez et al., 2021). Although this is a promising way to reduce biogenesis of EVs carrying tumor promoting factors, the differing biogenesis pathways of the EV subtypes poses a challenge for researchers trying to develop one drug that can block all EV biogenesis (Catalano and O'Driscoll, 2020). In the field, there are two distinct "categories" for drugs that inhibit EV biogenesis: one that affects EV trafficking (calpeptin, manumycin A, and Y27632) and the other that affects lipid metabolism (pantethine, imipramine, and GW4869). For example, within the category of drugs that affect EV trafficking falls calpeptin, a cysteine proteinase inhibitor. The anti-tumoral effects of calpeptin have been studied in a mouse xenograft model of prostate cancer, in which when mice were administered with calpeptin, they showed a significant reduction in tumor growth, a reduced vascularization, an increase in apoptosis, and reduced proliferation of cancer cells (Jorfi et al., 2015). The effects of the rest of the EV trafficking inhibitor drugs have yet to be studied in the context of GBM and EV interactions. Imipramine, a common anti-depression drug, has also been explored in the context of microvesicle release in glial cells and osteoblasts (Bianco et al., 2009; Deng et al., 2017). GW4869 is the only drug that has been studied in the context of GBM EVs, in which the results show that when GBM cells in vitro are treated with GW4869, their microRNA exosomal profiles change (Ipas et al., 2015). The field of EV biogenesis inhibitors needs to be explored further in the context of GBM but seems promising overall.

Another new method to use EVs as a therapeutic tool is to deliver purified EVs to a patient systemically. There have been promising studies conducted in vivo to look at the effects of systemic delivery of cell derived EVs on different murine disease models. Previous results show the ability of EVs carrying specific siRNAs or mRNAs to not only reach target tumor tissue (Ohno et al., 2013), but silence genes involved in neurodegenerative diseases (Alvarez-Erviti et al., 2011), when EVs are injected intravenously in mice. A more recent study published in 2021 showed that in rats, dendritic cell derived EVs that were administered nasally successfully entered the brain and were taken up mainly by oligodendrocytes, with little clearance by the liver (Pusic et al., 2021). These extremely promising results shown in vivo open the doors to potential systemic delivery of EVs in therapeutic trials in humans. To date, this is still a field in which scientists have only scratched the surface in understanding, so therefore only a few clinical trials have been completed.

6. Conclusion

EV derived from GBM or non-GBM cells in the TME are involved in tumor cell proliferation, invasion, malignancy, and drug resistance (Mathieu et al., 2019; Xia et

al., 2019). In the neurogenic niche, reciprocal communication between GSC and NSC occurs through soluble factors, direct cell contact, and EVs, resulting in changes that drive tumorigenesis (Wang et al., 2019). In the immune microenvironment, microglia and astrocytes react to the presence of tumor cells by changing their activation status and overall phenotype. This response occurs through multiple signals, including EVs (Bowen et al., 2011; Losurdo and Grilli, 2020). Finally, in the perivascular niche, the resident endothelial cells release EVs that interact with the tumor cells and contribute to GSC survival, progression, and angiogenesis (Bentolila et al., 2016; Burgett et al., 2016; Hu et al., 2016; Lathia et al., 2010; Man et al., 2014; Zhu et al., 2011).

Cancer cells are shown to release higher amounts of EVs compared to non-malignant cells, and these cancer EVs help communicate with other nearby cells, leading to promotion of tumorigenesis (Bebelman et al., 2018). Protocols for EV purification and the criteria for their characterization are still being optimized, with very promising advances. Novel technologies, like cell-specific labeling of biomolecules, will allow scientists to better understand the role of EVs in highly heterogeneous GBM tumors. Similarly, it will shed light on their use as diagnostic and therapeutic tools for GBM patients.

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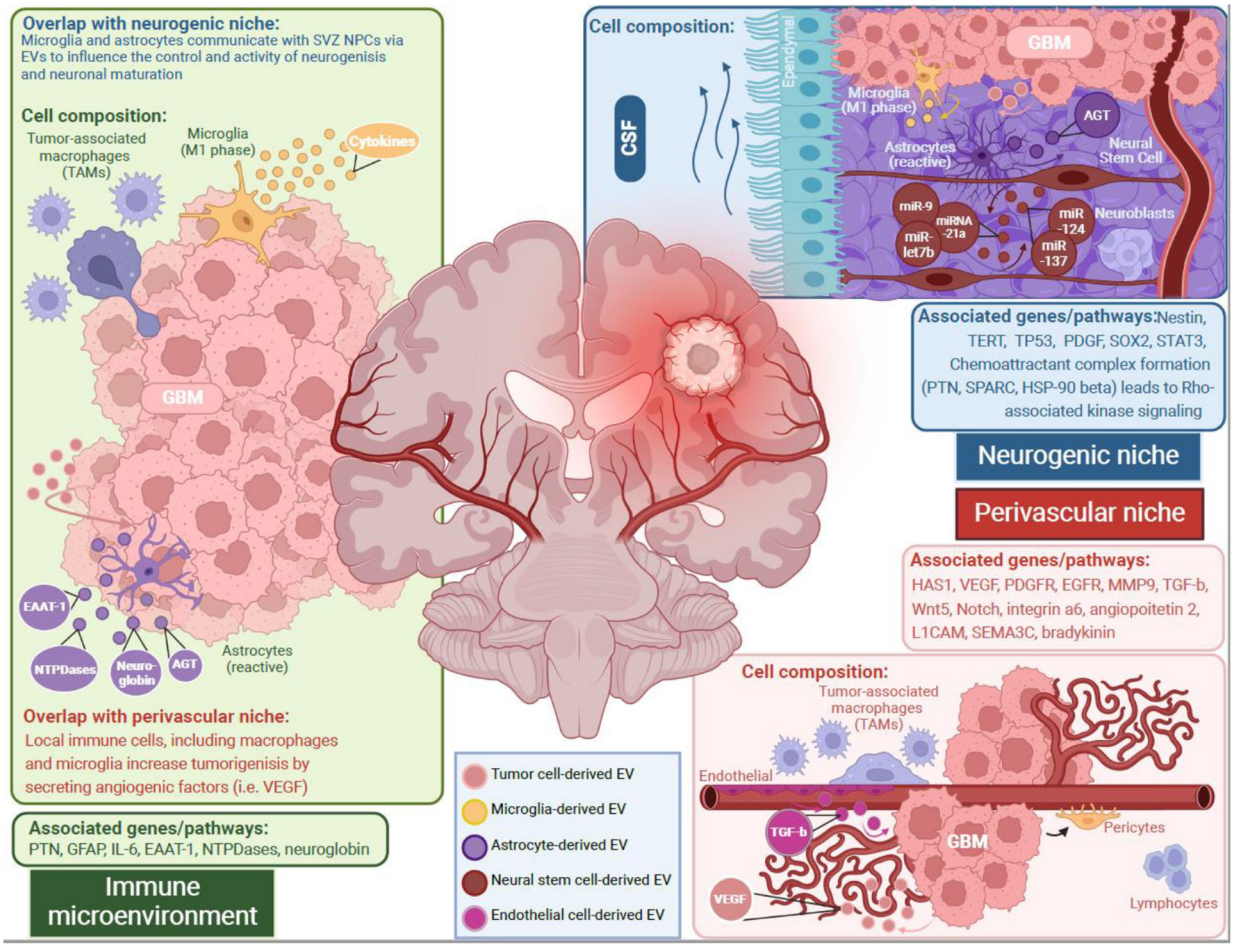

Figure 1. Extracellular vesicles participation in the communication between glioblastoma cells and non-cancer cells in the neurogenic, immune, and perivascular tumor microenvironment.

Each microenvironment presents niche-specific cell types and pathways that regulate tumor cell behavior. In each tumor microenvironment, there is reciprocal intercellular transport of proteins and microRNAs. Immune cells can release extracellular vesicles with cargo that impacts neural stem cell proliferation, such as cytokines from microglia extracellular vesicles which increase neural stem cell proliferation or EAAT-1 from activated astrocyte extracellular vesicles that decrease neural stem cell proliferation. These astrocytes can also increase tumor cell proliferation and survival with extracellular vesicles containing neuroglobin and alkylguanine DNA alkyltransferase respectively. Neural stem cells of the neurogenic niche can release extracellular that increase activated microglia and their cytokine release. Said neural stem cells also establish a crosstalk between themselves moderating quiescence and adult neurogenesis (miR-9, miRNA-21a, miR-let7b, miR-124, miR-137). Glioblastoma stem cells can manipulate this regulation by releasing extracellular vesicles that transform neural stem cells towards being cancerous. In the perivascular niche, endothelial cells have been seen to release extracellular vesicles containing TGF-β which prompts local glioblastoma stem cells towards differentiating into pericytes. Glioblastoma stem cells are also seen to recruit tumor-associated macrophages to increase tumor growth as well as supporting angiogenesis by increased VEGF.

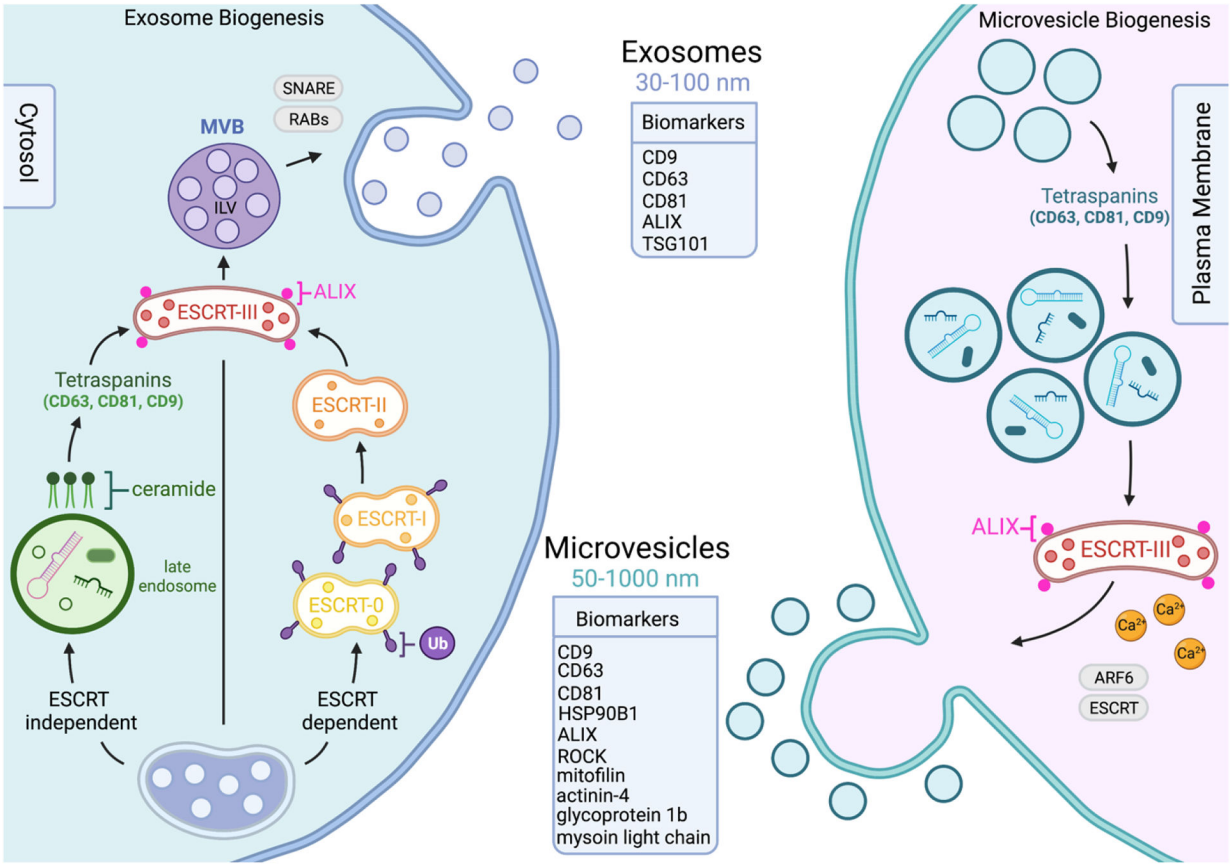

Figure 2. Extracellular vesicles biogenesis occurs by invagination or blebbing on the cell membrane originating different vesicle subtypes.

Extracellular vesicle biogenesis differs depending on the sub-population of vesicles in question. Exosomes range from 30–100nm in size, formed by plasma membrane invagination utilizing ESCRT-independent, shown to include ceramides and tetraspanin driven sorting, and ESCRT-dependent pathways, which gathers ubiquitylated cargo using ESCRT protein complexes. The release of exosomes derived from both pathways are influenced by SNARE and Ras-related proteins. Microvesicles are generally larger, ranging from 50–1000nm in size, and form through blebbing and budding on the plasma membrane. Microvesicles share components with exosome formation, including tetraspanins, however cargo in this case is determined by a component's lipid raft affinity and anchorage to plasma membrane. MVBs fuse with the plasma membrane and release the ILVs into the extracellular space. The budding and consequential release of microvesicles is influenced by Ca2+ levels, ESCRT pathway associated proteins, and ADP-ribosylation factor 6. Exosomes and microvesicles have distinct surface markers to help differentiate the two populations from each other.