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Review article

Glia-derived exosomes: Promising therapeutic targets

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ABSTRACT

Glia is an important component of the nervous system that is involved in neurotransmitter uptake, signal transduction, myelin synthesis, neurodevelopment, and immune response. Exosomes are extracellular vesicles that are secreted from certain types of cells, and are known to mediate glia function. Glia-derived exosomes (GDEs) can transport proteins, nucleotides and cellular waste, and exert both protective and toxic effects on the nervous system. GDEs promote glia-neuron communication, anti-stress responses, anti-inflammation and neurite outgrowth, and may also be involved in neurological disease such as glioma, glioblastoma, Alzheimer's disease, Parkinson disease and neuronal HIV infections. This review summarizes the current research on GDEs and their functions, with emphasis on their therapeutic potential.

1. Introduction

Glia are supporting cells of the nervous system, constituting almost 50% of the cellular population [1]. The different types of glia cells have distinct functions [2–4]; while astrocytes help neural generation and integrate neurological signals [5], the oligodendrocytes form myelin sheaths and sustain axon metabolism [6]. In addition, the microglia or the macrophages of the central nervous system (CNS) eliminate pathogens and regulate neuroinflammation [7]. Recent studies have demonstrated both protective and pathological effects of glia cells under different stimuli via the secretion of extracellular vesicles (EVs). The neural EVs are secreted by neurons, glial cells and even endovascular cells, and relay transport mediators involved in neuroinflammation, neural development and apoptosis [8]. They are mainly classified into the microvesicles with diameter between 100 - 1000 nm and exosomes measuring 50–100 nm (or 30–150 nm in some studies) [9,10]. They can also be differentiated on the basis of their contents and membrane markers.

Exosome formation begins with endocytosis of the plasma membrane, followed by inward budding into intraluminal vesicles (ILVs), and generation of a multivesicular body (MVB) via the endosomal sorting complex required for transport (ESCRT) pathway and the ESCRT independent ceramide pathway [9,11] (Fig. 1). In the nervous system, MVB formation involves intracellular prion proteins [12]. Fusion of the MVBs with the plasma membrane releases the exosomes in a $Ca2+$ influx-dependent manner [11,13,14]. Activation of the NMDA, AMPA and serotonin receptors via glutamate and 5-hydroxytryptamine increase the $Ca2+$ influx in neural cells [15,16]. Other pathways including Wnt-3a may also be involved in exosome secretion in the nervous tissues [17]. Exosomes release their cargo into recipient cells either via fusion with the cell membranes or through ligand/receptor-mediated endocytosis. Interestingly, although exosomes are loaded with cellular cargo including proteins, nucleotides and other molecules, their composition does not completely mirror that of the parent cells [18]. Exosomes of the nervous system are crucial for the cross-talk between neurons and glia cells [19]. They can also cross the brain-blood barrier (BBB) and enter the circulation, thus affecting the function of other organs [20–22]. Studies show that glia-derived exosomes (GDE) mediate the functions of the parent cells, and also drive pathological conditions like glioma, Alzheimer's disease (AD), Parkinson disease (PD), human immunodeficiency virus (HIV) infection, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) by transporting mutated genes, damaged proteins and pathogens. In this review, the different functions of GDEs have been discussed in the context

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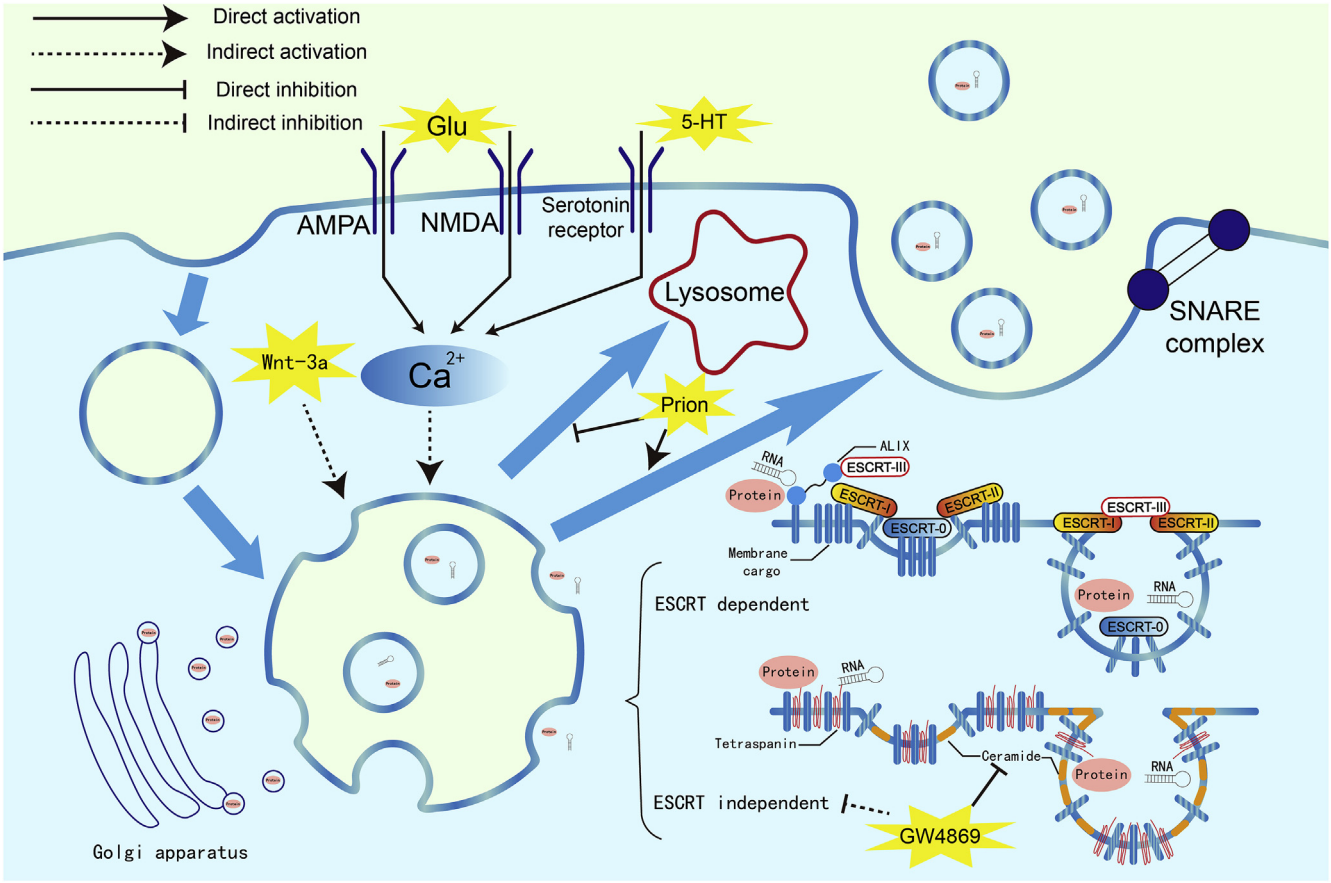

Fig. 1. The mechanisms involved in the formation of GDEs. As with exosomes derived from other types of cells, GDEs also originate from endosomes. The inward budding of endosomes form MVBs via ESCRT dependent and independent pathways. The former requires ESCRT-0, I, II and III, and the latter is dependent on tetraspanins (CD9, CD63 and CD81) and ceramide. The MVB then attaches to the plasma membrane and releases GDEs with the aid of SNAREs. Glu, 5-HT, Wnt-3a, Prion and GW4869 regulate GDE release through different pathways.

of their therapeutic value.

2. GDEs have neurotransmitter disposing effect

GDEs maintain neural homeostasis via neurotransmitter degradation and re-uptake, which is essential for the normal functioning of the nervous system. Potolicchio et al. found that the aminopeptidase CD13 was highly expressed in microglia-derived exosomes (MDEs), and was transported into targeted cells wherein it cleaved leucine- and methionine-enkephalins neuropeptides, thereby blocking the activation of opioid receptors [23]. Excitatory amino-acid transporters (EAATs) are crucial for re-uptake of extracellular glutamate by the astrocytes. Gosselin et al. found that the amount of EAATs increased in spinal astrocyte-derived exosomes (ADEs) after spared nerve injury (SNI), resulting in [3H]-aspartate re-uptake [24]. The elimination of excessive amounts of neurotransmitters by the exosomes likely ameliorates the pain during SNI.

Potential therapeutic value: Neurotransmitter imbalance is the pathological basis of neuropsychic diseases like schizophrenia and depression [25], as well as neurodegenerative disorders like PD [26]. Therefore, administration of GDEs containing neurotransmitters or their inhibitors may have therapeutic value for these conditions.

3. Neuro-regenerative effects of GDEs

GDEs can promote neural regeneration by stimulating neurite outgrowth (Table 1). Neurites are neuronal projections including axons and dendrites. In the immature nervous system, neurites originate from the soma of developing neurons and form a network between neurocytes [27]. They are damaged during neural injury, and the outgrowth of newly formed neurites is a sign of neuro-regeneration. Wang et al. found that ADEs promoted neurite outgrowth by transporting the neurotrophic glycoprotein synapsin I. Co-culture of synapsin I-enriched astrocytes with hippocampal neurons significantly improved the neurite outgrowth from the latter. High KCl concentration or oxidative stress increase synapsin I release from exosomes, and thus promote neurite outgrowth [28]. ADEs also aid neurite outgrowth by transporting vimentin, which is essential for the neuro-regenerative effects of the *Clostridium botulinum* C3 exoenzyme (C3bot), a bacterial ADP-ribosyltransferase. Adolf et al. found that ADEs derived from wild-type astrocytes contained vimentin which enhanced the interaction of C3bot with mouse brain synaptosomes, and improved axonal outgrowth in a rat model of spinal cord injury (SCI). However, exosomes derived from vimentin-negative astrocytes failed to induce neuro-regeneration [29]. Hira et al. further demonstrated that the neurotrophic effect of ADEs released under ischemic conditions was dependent on blocking semaphorin 3 A, an extracellular molecule that inhibits axonal outgrowths. ADEs released under oxygen and glucose deprivation (OGD) only slightly improved axon outgrowth, whereas exosomes derived from OGD-preconditioned and semaphorin 3 A inhibitor-treated astrocytes significantly elongated axons. The underlying mechanism is not completely clear, but may be related to the expression of prostaglandin D2 synthase [30]. MDEs can also exhibit neuro-regenerative effects under specific stimuli. In a study by Huang et al., miR-124-3p-enriched MDEs enhanced neurite outgrowth both *in vitro* after scratch injury as well as *in vivo* following traumatic brain injury (TBI) in mice. The exosomal

Table 1
Mechanisms of GDEs.

Number	Author	Year	Source Cell	Stimulation	Effective Component	Change of components after stimulation	Effect
1	Potolicchio [23]	2005	Microglia	N/A	CD13, a aminopeptidase which degrades enkephalins	N/A	Neural homeostasis
2	Gosselin [24]	2013	Astrocyte	SNI	EAATs	Increased	Neural homeostasis
3	Wang [28]	2011	Astrocyte	N/A	Synapsin I	N/A	Neural promotive and anti-stress effects
4	Adolf [29]	2018	Astrocyte	N/A	Vimentin	N/A	Neural promotive effect
5	Hira [30]	2018	Astrocyte	Ischemia and semaphorin 3A inhibitor treatment	N/A	N/A	Neural promotive effect
6	Huang [31]	2018	Microglia	TBI	miR-124-3p	Increased	Neural promotive and anti-inflammatory effect
7	Raffo-Romero [32]	2018	Microglia	N/A	TGF-β1	N/A	Neural promotive effect
8	Bianco [33]	2009	Microglia	ATP	IL-1β	Increased	Pro-inflammation
9	Cunda [34]	2016	Microglia	LPS	miR-155	Increased	Pro-inflammation
10	Vinuesa [35]	2018	Microglia	Palmitate	N/A	Increased	Pro-inflammation
11	Yang [36]	2018	GBM	N/A	miR-214-5p	Increased	Pro-inflammation
12	Sobue [37]	2018	Astrocyte	systemic immune activation and AAV infection	MHC I, H-2D	Increased	Pro-inflammation
13	Guo [38]	2019	Astrocyte	EAE	αB-crystallin	Increased	Anti-inflammation
14	Krämer-Albers [5]	2007	Oligodendroglia	Increasing Ca^{2+} concentration	Anti-stress enzymes, PLP, CNP, MBP, MOG	Increased	Anti-stress and elimination of cellular wastes
15	FrÜhbeis [15]	2013	Oligodendroglia	Glutamate and activated NMDA or AMPA	N/A	N/A	Anti-stress
16	Fröhlich [39]	2014	Oligodendroglia	OGD	SOD, Catalase	Increased	Anti-stress
17	Taylor [40]	2007	Astrocyte	Hyperthermia	Hsp/c70	Increased	Anti-stress
18	Guitart [41]	2016	Astrocyte	OGD	PrP	Increased	Anti-stress
19	Tamboli [7]	2010	Microglia	Statin	IDE	Increased	Elimination of cellular wastes
20	Nafar [43]	2016	Astrocyte	Aβ	HspB1	Increased	Elimination of cellular wastes
21	Bakhti [46]	2011	Oligodendroglia	Neuronal conditioned medium	PLP, CNP, MAG, MOG	Reduced	Elimination of cellular wastes
22	Fitzner [47]	2011	Oligodendroglia	N/A	PLP, MOG	N/A	Elimination of cellular wastes

miR-124-3p exerted its neurogenerative effects by targeting PDE4B and inhibiting the mTOR pathway [31]. Another study showed that MDEs increased the length of neurite outgrowths in leech neurons, likely via TGF-β1 overexpression [32].

Potential therapeutic value: The neuro-regenerative and neurotrophic effects of GDEs have been demonstrated in rodent models of TBI, SCI and ischemic stroke [29–31], and may show similar therapeutic effects in strokes, neural trauma and neurodegenerative diseases.

4. Pro or anti-inflammatory functions of GDEs

Neuroinflammation is a common cause of additional neural damage following primary injury. GDEs regulate neuroinflammation by transporting relevant proteins and miRNAs (Table 1).

Microglia can be activated by various stimuli and initiate an inflammatory response, which may involve the secretion of MDEs containing cytokines or pro-inflammatory miRNAs. Bianco et al. found that the exosomes secreted by ATP-stimulated microglia were enriched in IL-1β [33], while Cunha et al. detected the pro-inflammatory miR-155 in exosomes derived from lipopolysaccharide (LPS)-stimulated microglia [34]. These mediators were transported via MDEs and increased neuroinflammation. High-fat diet is another stimulus for the secretion of pro-inflammatory MDEs. Vinuesa et al. found that neuroinflammation can be simulated *in vitro* by culturing microglia with palmitate, and the exosomes derived from these cells significantly reduced the proportion of mature dendritic spines relative to the immature spines on dendritic segments of hippocampal neurons. This morphological change has been observed *in vivo* during neuroinflammation, which underscores the pro-inflammatory effect of high-fat induced MDEs [35]. Yang et al. found that the pro-inflammatory miR-214-5p was overexpressed in glioblastoma (GBM) cells and GBM-derived exosomes (GMBDEs), and activated primary microglia [36]. Sobue et al. showed that ADEs released under systemic immune activation and adeno-associated virus (AAV) infection were enriched in histocompatibility complex class I (MHC I) and its encoding gene H-2D, which activated the microglia by upregulating pro-inflammatory cytokines and impaired neuronal function in mice [37].

GDEs can also exhibit anti-inflammatory effects under certain conditions. Huang et al. found that the level of miR-124-3p increased in exosomes derived from microglia cultured with brain extracts of TBI mice, which in turn increased the ratio of the anti-inflammatory M2 microglia and ameliorated inflammation in a neuron scratch-injury model [31]. Furthermore, Guo et al. detected the anti-inflammatory heat shock protein αB-crystallin in the exosomes released from astrocytes of mice with experimental autoimmune encephalomyelitis (EAE) [38], indicating that these ADEs could be the basis of the anti-inflammatory effect of astrocytes.

Potential therapeutic value: The anti or pro-inflammatory effects of GDEs depend on their cargoes, which can be analyzed after extracting GDEs from the serum, plasma or cerebrospinal fluid. Accordingly, the secretion of anti or pro-inflammatory GDEs can be respectively enhanced or reduced. Furthermore, these GDEs are potential therapeutic targets for neural infection, immune encephalomyelitis and post-injury inflammation in stroke and neural trauma.

5. Anti-stress effect of GDEs

Cellular stresses, including oxidative, hypoxic and toxic stresses, result in pathological changes in the nervous system. Various bioactive substances and neuroprotective chemicals alleviate damage to the nervous system by neutralizing cellular stress. Several types of GDEs are also known to exert an anti-stress effect during neural injuries (Table 1).

Oligodendrocyte-derived exosomes (ODEs) balance myelin generation and degradation. In 2007, Eva-Maria et al. analyzed the proteomes of ODEs, and identified several anti-stress enzymes like dihydropyrimidinase-related protein and peroxiredoxin [2]. Frühbeis et al. observed that ODEs reversed the decrease in neuronal activity following H_2O_2 administration and nutrient deprivation *in vitro* [15]. Consistent with this, Fröhlich et al. detected the anti-oxidative enzymes superoxide dismutase 1 (SOD1) and catalase in ODEs, and found that they increased neuronal survival and alleviated cellular stresses by activating the AKT and ERK pathways [39]. Furthermore, Taylor et al. showed that the heat shock protein c70 (Hsp/c70) levels increased significantly in the astrocytes under hyperthermic conditions, and were released into microenvironment via ADEs that protected the adjacent neurons [40]. ADEs also harbor the oligomannose-binding protein synapsin I, which exerts a neuroprotective effect following H_2O_2 exposure or oxygen/glucose deprivation [28]. Guitart et al. detected the neuroprotective Prion protein (PrP) in the exosomes of astrocytes cultured under OGD conditions, and the PrP-enriched ADEs significantly increased the survival of neurons exposed to H_2O_2. Pretreatment of ADEs with phosphatidylinositol specific phospholipase C cleaved the exosomal PrP and abolished its antioxidant effects [41].

Potential therapeutic value: Cellular stress is a common cause of neural dysfunctions including ischemic, traumatic, hyperthermic, toxic injuries. The anti-stress effect of GDEs indicate their potential as therapeutic agents against ischemic stroke or chronic ischemic encephalopathy. *In vivo* experiments are needed to confirm the anti-stress effects of GDEs.

6. GDEs remove cellular waste products

Cellular waste products like misfolded proteins disrupt cellular metabolism and functions, and are therefore eliminated by lysosomal degradation or exosomal secretion. Neurons dispose their waste by secreting exosomes and transporting them to the microglia for degradation [42]. Furthermore, microglia also release exosomes containing enzymes or other proteins like insulin-degrading enzyme (IDE) and HspB1 that eliminate the waste products secreted by neurons [4,43] (Table 1). The non-degraded products are returned to the extracellular environment or neurons, which may initiate or aggravate a pathological condition [44]. Over-produced cellular components are also a type of cellular waste (Table 1). In oligodendrocytes for example, myelin overexpression leads to dysmyelination and other neurological disorders [2,45]. ODEs can dispose the excess myelin components and the oligodendroglial membranes, thus inhibiting the surface expansion of oligodendrocytes. In fact, ODEs harbor abundant myelin related proteins such as myelin proteolipid protein (PLP), 2′3′-cyclic-nucleotide-phosphodiesterase (CNP), myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) [2]. Consistent with this, increased secretion of ODEs is correlated with significantly decreased myelination. ODEs also inhibited the surface expansion of oligodendrocytes cultured in neuronal conditioning medium through the Fyn-RhoA pathway [46]. Fitzner et al. showed that ODEs are specifically taken up by the microglia, which are the final destination of the overproduced myelinic components [47].

Potential therapeutic value: Microglia eliminate cellular waste by secreting MDEs and internalizing waste-containing exosomes released from neurons or glia. Thus, enhancing the waste disposal capacity of microglia without inducing inflammation is a potential therapeutic strategy against some neuronal diseases. ODEs enriched in myelinic components have been detected in the sera of patients with multiple sclerosis. Therefore, inhibiting secretion of ODEs can be of therapeutic value.

7. Disease-related GDEs

GDEs can be a double-edged sword in many neurological diseases. It is involved in the development of glioblastoma, AD and HIV-associated neurological disorders (HANDs), and may be a protective factor in other neurological diseases (Table 2).

Table 2
Role of GDEs in GM, AD, HANDs, PD, multiple sclerosis, Japanese encephalitis, Huntington disease, morphine addiction and choroidal neovascularization.

Number	Author	Year	Source Cell	Stimulation	Effective Component	Change of components after stimulation	Effect
1	Skog [49]	2008	GBM	N/A	mRNA, miRNA and proteins (EGFRvIII) related to tumor genesis	N/A	Tumor genesis
2	Oushy [50]	2018	GBM	N/A	N/A	N/A	Tumor genesis
3	Al-Nedawi [51]	2008	GBM	N/A	EGFRvIII	N/A	Tumor genesis
4	Murigoci [52]	2018	Microglia	LPS	N/A	N/A	Anti-tumor
5	van der Vos [53]	2016	GBM	N/A	miR-451 and miR-21	N/A	Tumor genesis
6	Guo [54]	2018	GM	Hypoxia	miR-10a and miR-21	Increased	Tumor genesis
7	Bian [55]	2019	GM	N/A	lncRNA-ATB	N/A	Tumor genesis
8	Guescini [3]	2010	GBM	N/A	mtRNA	N/A	Tumor genesis
9	Zeng [57]	2017	GBM	N/A	N/A	N/A	Chemoresistance of tumor
10	Yu [58]	2018	Reactive astrocyte	MGMT transgenosis	MGMT mRNA	Increased	Chemoresistance of tumor
11	Wang [62]	2012	Astrocyte	Aβ	Ceramide, PAR-4	Increased	AD development
12	Dinkins [63]	2016	Astrocyte	Aβ	Ceramide	Increased	AD development
13	Asai [44]	2015	Microglia	Pre-aggregated protein tau	tau	Increased	AD development
14	Chiarini [64]	2017	Astrocyte	Aβ	tau, p-tau	Increased	AD development
15	Nikitidou [65]	2017	Variety of glial cells	N/A	Apo E	Increased	AD development
16	Tamboli [4]	2010	Microglia	Statin	IDE	Increased	AD inhibition
17	Nafar [43]	2016	Astrocyte	Aβ	HspB1	Increased	AD inhibition
18	Hu [67]	2012	Astrocyte	morphine, HIV Tat	miR-29b	Increased	HANDs development
19	Rahimian [68, 69]	2016	Astrocyte	Tat transgene	Tat, miR-132	Increased	HANDs development
20	Raymond [71]	2016	Microglia	Nef transfection	Nef	Increased	HANDs development
21	Pužar Dominkuš [72]	2017	Astrocyte	Nef transfection	Nef	Increased	HANDs development
22	Chang [73]	2013	Microglia	α- synuclein	MHC class II molecules, membrane TNF-α	Increased	PD development
23	Ohmichi [74]	2018	Variety of glial cells	N/A	N/A	Increased	PD biomarker
24	Basso [75]	2013	Astrocyte	N/A	mutant copper-zinc superoxide dismutase	N/A	Amyotrophic lateral sclerosis
25	Podbielska [76]	2016	Oligodendroglia	TNF-α, IFN-γ	Ceramide	Increased	Cerebral multiple sclerosis
26	Mukherjee [77]	2018	Microglia	Japanese Encephalitis Virus	let-7a/b	Increased	Japanese Encephalitis
27	Hong [78]	2017	Astrocyte	Mutant huntingtin	Protective HSPs	Reduced	Huntington disease
28	Ou [79]	2018	Astrocyte	Sinomenine	N/A	N/A	Morphine addiction
29	Hajrasouliha [80]	2013	Astrocyte	N/A	Endostatin	N/A	Choroidal neovascularization inhibition

7.1. GM and GBM

Gliomas (GM) are the most common primary tumor of the brain, of which glioblastoma (GBM) is the most aggressive type [48]. Exosomes derived from GM cells (GMDEs) are correlated to GM initiation and progression, as well as changes in the microenvironment, and induce a tumorigenic phenotype in the adjacent glial cells. GMDEs can phenotypically alter other neural cells by transporting cytokines and regulating the downstream signal pathways. They are also known to enhance angiogenesis, which provides nutrients to the growing tumor. Al-Nedawi et al. demonstrated *in vitro* angiogenesis and GM cell proliferation by the GBMDEs, which was attributed to the presence of several angiogenic mediators like angiogenin, FGF-α, IL-6, IL-8, TIMP-1, VEGF and TIMP-2 in these exosomes [49]. Consistent with this, Oushy et al. found that GBMDEs promoted the secretion of IFN-γ, IL-12, IL-1α, IL-1β, IL-8, CXCL10 and CXCLC5 from normal astrocytes, and increased their proliferation rates and induced malignant transformation via the MAPKs, JNK, ERK, AKT and p53 pathways [50]. GMDEs are also involved in crosstalk between GM cells, which further increases malignancy of the tumors. Epidermal growth factor receptor vIII (EGFRvIII) is a mutated form of EGFR that indicates worse prognosis in GM. The GMDEs transport EGFRvIII from the GM cells expressing this protein to those lacking it, wherein it activates the MAPK and AKT pathways and upregulates VEGF, Bcl-x and p27, all of which promote malignancy of recipient GM cells [51]. In contrast, Murgoci et al. observed that the invasion and migration of GM cells decreased in the presence of exosomes derived from LPS-stimulated microglia [52].

GMDEs can also transport mRNAs, miRNAs and lncRNAs, and induce or inhibit the expression of oncogenes and tumor suppressors. Several mRNAs related to cell proliferation, immune response, cell migration and histone modification have been identified in GBMDEs [49]. In addition, van der Vos et al. found that GBMDEs transported miR-451 and miR-21 into microglia, wherein they inhibited the anti-oncogene c-Myc and increased secretion of GM-promoting cytokines [53]. The miRNAs in GMDEs also exert an immunosuppressive effect by activating myeloid-derived suppressor cells (MDSCs), which enable the GM cells to escape the host immune system. The expression of miR-10a and miR-21 increased in the GMDEs under hypoxic conditions, and suppressed RAR-related orphan receptor alpha (RORA), phosphatase and tensin homologs (PTEN) in the MDSCs, thereby enhancing their proliferation and activation [54]. Furthermore, Bian et al. found that GMDEs transported the TGF-β-induced lncRNA-ATB to adjacent astrocytes and activated them by inhibiting the function of miR-204-3p. The activated astrocytes in turn promoted migration of GM cells [55]. Mitochondrial DNA (mtDNA) was detected in GBMDEs by Guescini et al. [3], and another study showed that high copy numbers of mtDNA in GM tissues predicted favorable prognosis [56]. Thus, presence of mtDNA-enriched GBMDEs is an indicator of poor prognosis since they can transport mutated mitochondrial genes to target cells and promote tumor progression.

Zeng et al. recently demonstrated the role of GBMDEs in the chemoresistance of GBMs. The PTPRZ1–MET fusion protein (ZM) induces a more malignant form of GBM by enhancing the phosphorylation of the oncogenic MET. The ZM + GBM cells transported MET and p-MET into cells lacking the fusion protein via exosomes and induced a more invasive phenotype. In addition, GBM cells treated with exosomes derived from ZM + GBMs developed resistance to temozolomide (TMZ), as did patients harboring the fusion protein [57]. Yu et al. similarly reported

that exosome-mediated transfer of O6-alkylguanine DNA alkyltransferase (MGMT) mRNA from the MGMT + astrocytes into MGMT- glioma cells induced TMZ resistance in the latter [58].

Potential therapeutic value: GMDEs or GBMDEs can enhance the malignant phenotype by enhancing proliferation, invasion and chemoresistance of the tumor cells. Therefore, inhibiting their secretion from tumor tissues can be a promising therapeutic strategy, although more studies are needed.

7.2. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that manifests as cognitive and memory dysfunction. The pathological basis of AD is the extracellular aggregation of β-amyloid (Aβ) into plaques. Studies show that Aβ can be released into exosomes [59], indicating an important role of the latter in AD progression. In addition, GDEs can also aggravate the condition by transporting ceramide and prostate apoptosis response 4 (PAR-4) protein. Ceramide is a peptide generated by acid sphingomyelinase (nSMase) that induces apoptosis in astrocytes [60]. PAR-4 also has a proven role in Aβ-related apoptosis [61]. Wang et al. found that Aβ-stimulated astrocytes secrete exosomes containing PAR-4 and ceramide that induce apoptosis of recipient astrocytes, indicating a potential mechanism of neurodegeneration in AD [62]. Dinkins et al. further confirmed that ceramide-enriched ADEs induced the aggregation of $A\beta_{42}$, while nSMase2 knockdown in 5XFAD mice significantly decreased the release of brain exosomes, exosomal ceramide levels and Aβ aggregation, and improved cognition [63].

Protein tau is a microtubule-associated protein, and aggregation of its phosphorylated form results in neurofibrillary tangles (NET), another pathological change associated with AD. Asai et al. showed that microglia engulfed and then secreted extracellular pre-aggregated protein tau into MDEs, which were taken up by neurons and led to the formation of intracellular NETs [44]. GDEs can aggravate the pathological effects of Aβ and p-tau during AD progression. Chiarini et al. detected high levels of tau and p-tau in Aβ-treated astrocytes, which was transported to adjacent cells via the ADEs [64]. Apolipoprotein E and several complementary proteins detected in GDEs might also contribute to the pathology of AD [65]. Further experiments are needed to determine the function of these exosomal components.

Under certain conditions, GDEs also exhibit a protective effect during AD. For instance, IDE has the ability to degrade extracellular Aβ and is frequently detected in MDEs. Tamboli et al. found that the number of MDEs and the level of exosomal IDE increased significantly after statin treatment [4]. Furthermore, Nafar et al. showed that HspB1 levels increased in the exosomes derived from Aβ-stimulated astrocytes, and significantly cleared the Aβ aggregates [43].

Potential therapeutic value: GDEs may contribute to the progression of AD by transporting Aβ, protein tau and other neurotoxic components. Although it is difficult to inhibit the formation of Aβ and protein tau, the other toxins are potential therapeutic targets. In addition, increasing the level of Aβ and protein tau degrading enzymes in the GDEs may have a potential therapeutic value in AD.

7.3. HIV-associated neurological disorders (HANDs)

HIV is the causative agent of the acquired immunodeficiency syndrome (AIDS). In the advanced stages of AIDs, some patients develop HANDs that manifest as hypophrenia, unconsciousness and chronic headaches. GDEs contribute to the progression HANDs by transporting the Tat and negative factor (Nef), proteins. Tat is a transactivation protein of HIV that can enhance viral transcription and aggravate HANDs [66]. Hu et al. found the level of the neurotrophic platelet-derived growth factor (PDGF-B)-targeting miR-29b increased significantly in the exosomes derived from astrocytes stimulated with morphine and Tat. Accordingly, the PDGF-B levels decreased significantly in neural progenitor cells cultured with these ADEs, and reduced cell viability [67]. Rahimian et al. demonstrated that Tat-expressing transgenic astrocytes transported the protein via exosomes, which shortened the neurites and decreased neuronal survival rate [68]. The same group detected high levels of miR-132 is the exosomes of Tat-expressing astrocytes, which could be an indirect pathway of Tat-induced neuropathological changes [69]. Nef is an accessary protein of HIV associated with its replication capacity and pathogenesis [70]. Raymond et al. showed that Nef was released by the exosomes derived from Nef-transfected microglia. The Nef + MDEs impaired the tight junction function of endothelial cells by downregulating the junction proteins. Furthermore, microglia stimulated with the Nef + MDEs secreted high levels of pro-inflammatory cytokines like RANTES, IL-8, IL-12 and IL-6, which impaired the function of BBB, reduced *trans*-epithelial electrical resistance and increased BBB permeability [71]. Pužar Dominkuš et al. also reported exosomal release of Nef from the Nef-expressing astrocytes, with the latter secreting significantly more exosomes compared to the normal cells [72]. The Nef-bearing ADEs most likely aggravate HIV infection by spreading this protein across neural cells.

Potential therapeutic value: GDEs aggravate HANDs by transporting pathogenic proteins like Tat and Nef, as well as miRNAs and cytokines. Since the exact mechanism of HANDs is unclear, the therapeutic value of GDEs in HANDs cannot be determined at present, although they may be useful as a diagnostic tool.

7.4. Other neurological disorders related to GDEs

7.4.1. Role of neurotoxic GDEs in neurological disorders

GDEs also show neurotoxic effects during progression of Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), cerebral multiple sclerosis (MS) and viral encephalitis. Chang et al. showed that the PD-related neurotoxin α-synuclein enhanced the secretion of MDEs expressing high levels of MHC II and membrane TNF-α, which in turn induced apoptosis in adjacent neurons [73]. Ohmichi et al. also indicated that the increased secretion of GDEs during PD is a potential biomarker [74]. In addition, ADEs transport mutant copper-zinc superoxide dismutase (CuS-SOD) to motor neurons and induce apoptosis during ALS progression [75], whereas the level of ceramide-enriched ODEs is increased by the pro-inflammatory TNF-α and IFN-γ in cerebral MS and activates apoptotic pathways [76]. Japanese Encephalitis Virus infection induced the expression of let-7a/b in microglia, and the let-7a/b-enriched MDEs induced caspase activation and apoptosis in the recipient neurons [77].

7.4.2. Role of neuroprotective GDEs in neurological disorders

GDEs also play neuroprotective role in many diseases. During the progression of Huntington disease, ADEs containing HSPs can ameliorate the neurotoxicity of misfolded proteins. However, the mutant huntingtin protein decreases secretion of these ADEs and inhibits the expression of the protective αB-crystallin [78]. Morphine increases the intracellular levels of cAMP, Ca^{2+}, and phosphorylated NMDAR1, CAMKII and CREB, which could be the basis of hippocampal morphine addiction. The exosomes released by sinomenine-treated astrocytes reduce the aforementioned factors and have an ameliorative effect on the addictive effects of morphine [79]. Similarly, exosomes released from retinal astrocytes express the anti-angiogenic endostatin, which inhibits choroidal neovascularization [80].

8. Discussion and outlook

GDEs are involved in neural homeostasis, neural regeneration, inflammation regulation, anti-stress effect, cellular waste disposal, as well as neurodegenerative diseases. Since the glial cells are exclusively located in the nervous structures, the targets of GDEs are always neurons or other glia. In addition, the GDEs carry complex cargoes, including enzymes, structural proteins, membrane proteins, mRNAs, miRNAs, lncRNAs and mtDNA, from the parent cells, and therefore tend to

Table 3
GDE-related neurological disorders that proved by experiments.

Number	GDE-related neurological disorders	Relative mechanisms of GDEs	References of *in vitro* researches	References of *in vivo* researches
1	SNI	Neurotransmitter disposing effect	[24]	[24]
2	SCI	Neural promotive effect	[29]	[29]
3	Ischemic Stroke (MCAO)	Neural promotive effect	[30]	[30]
4	TBI	Neural promotive effect, anti-inflammatory effect	[31]	[31]
5	High-fat diet induced neural injury	Pro-inflammatory effect	[35]	[35]
6	GM or GBM	Pro-inflammatory, tumor genesis, enhance medical resistance, anti-tumor effects	[3, 36, 49, 50, 51, 53, 54, 55, 57, 58]	[49] (clinical)
7	Systemic immune activation induced brain disease	Pro-inflammatory	[37]	[37]
8	Autoimmune encephalomyelitis	Anti-inflammatory	[38]	[38]
9	Hyperthermic neural injury	Anti-stress	[40]	-
10	AD	Waste disposing, aggregation of Ab and protein tau	[4, 43, 44, 62, 63, 64, 65]	[63]
11	HANDs	Pro-inflammatory effect, BBB impariment	[67, 68, 69, 71, 72]	[71]
12	PD	Apoptotic effect	[73, 74]	-
13	ALS	Pro-inflammation	[75]	-
14	MS	Pro-inflammation	[76]	-
15	Viral encephalitis	Apoptotic effect	[77]	-
16	Huntington disease	Prevent protein misfolding	[78]	-
17	Morphne addiction	Inhibition of addictive pathways	[79]	-
18	Choroidal neovascularization	Transporting antiangiogenic components	[80]	-

mirror the function of the latter. For instance, ADEs usually exert supportive and transport effects, MDEs are involved in neuroinflammation and waste elimination, while ODEs are often involved in myelin sheath adjustment and neural protection. The microenvironment stimuli also affect the functions of GDEs. Although only three types of glia are present in the CNS, the exosomes derived from these cells have highly diverse effects depending on the stimuli. GDEs can also cross the BBB on account of their lipid membranes and enter the bloodstream, resulting in their uptake by distant organs, which leads to systemic effects [22].

We found 41 studies that correlated GDEs with 18 distinct neurological disease (Table 3). However, most studies have focused on the pathological or protective mechanisms of GDEs and not on their therapeutic value. The function of GDE in one disease may be potentially therapeutic in another. For instance, in neural ischemia or traumatic diseases, GDEs exert regenerative, pro- or anti-inflammatory and anti-stress effects. Therefore, further studies are needed to analyze the common and specific functions of GDEs in different diseases, in order to identify the therapeutic targets. Furthermore, very few studies on GDEs have validated their findings in *in vivo* models. Only 10 studies included in this review confirmed the GDE-related mechanisms in animal models or patients, including experimental models of SNI, SCI, MCAO, TBI, GBM and 5XFAD, and illustrated the therapeutic value of GDEs in spinal injury, cerebral ischemia or trauma and AD [24,29–31,35,37,38,49,63,71]. This means only neurotransmitter disposing, neuro-regenerative, anti-inflammatory, and Aβ transporting mechanisms of GDEs have been proved *in vivo*. Still, few studies directly administered the GDEs to the subjects due to technical difficulties. Studies show that systemically administered exosomes crossed the BBB and induced neuroprotective effects [81]. Another study reported beneficial outcomes of intranasal delivery of exosomes [82]. Nevertheless, considerable efforts are required to improve the efficacy of exogenously delivered GDEs.

The therapeutic use of GDE is still a pre-clinical concept, besides the difficulty of exogenous GDEs administration, there are several other challenges at present regarding clinical translation. The nSMase inhibitor GW4869 inhibits the release of ceramide-enriched GDEs and is therefore a potential therapeutic option against AD [33,83]. However, GW4869 is non-selective and may also target the beneficial exosomes [84], resulting in possible side effects and thus limiting its clinical potential. In addition, this inhibitor may also interfere with other cellular process such as apoptosis, which may disturb us to judge if it is the reduction of GDEs that account for the outcomes. Moreover, it is not recommended to administer GDEs *in vivo* to treat a specific disorder since their cargoes can have more systemic consequences. It is thus imperative to determine the specific conditions/stimuli that enrich beneficial GDEs. For instance, adjusting the conditions of glial cell culture can induce the loading of the desired components into exosomes, which can be selectively extracted. These extracted GDEs and beneficial conditions may have great potential therapeutic value.

In conclusion, GDEs exert both positive and negative effects on neurological processes, and identifying the specific conditions that induce beneficial GDEs, as well as the precise mechanisms of these exosomes, can be of significant therapeutic value. Although many of the mechanisms are just proved *in vitro*, there is still possibility for them to be proved *in vivo* and applied to clinical practice with the help of new technics and further experiments.

Ethical approval statement

Ethical approval is not applicable in our manuscript.

Declaration of Competing Interest

All authors declared that they have no conflicts of interest to this work.

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