REVIEW

Exosomes as mediators of neuron-glia communication in neuroinflammation

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Abstract
In recent years, a type of extracellular vesicles named exosomes has emerged that play an important role in intercellular communication under physiological and pathological conditions. These nanovesicles (30–150 nm) contain proteins, RNAs and lipids, and their internalization by bystander cells could alter their normal functions. This review focuses on recent knowledge about exosomes as messengers of neuron-glia communication and their participation in the physiological and pathological functions in the central nervous system. Special emphasis is placed on the role of exosomes under toxic or pathological stimuli within the brain, in which the glial exosomes containing inflammatory molecules are able to communicate with neurons and contribute to the pathogenesis of neuroinflammation and neurodegenerative disorders. Given the small size and characteristics of exosomes, they can cross the blood-brain barrier and be used as biomarkers and diagnosis for brain disorders and neuropathologies. Finally, although the application potential of exosome is still limited, current studies indicate that exosomes represent a promising strategy to gain pathogenic information to identify therapeutically targets and biomarkers for neurological disorders and neuroinflammation.

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Introduction
Intercellular communication is mediated by direct cell-to-cell contact and by the cell secretome (Meinken et al., 2015) that releases protein and nonprotein components (e.g., lipids or RNAs) via endosomal-exocytosis. Among the most important components of the cell secretome are the exosomes, which are membrane-derived microvesicles (30–150 nm) secreted by almost every cell type and present in numerous body fluids. Exosomes were first discovered by Pan and Johnstone in 1983, when they observed how transferrin receptors, associated with small 50 nm vesicles, were released from maturing blood reticulocytes into the extracellular space by a receptor-mediated endocytosis and recycling process (Harding et al., 2013). Since that time, the study of extracellular vesicles (EVs) has improved and evolved, and today we are able to differentiate three groups of EVs according to their size and biogenesis: exosomes (30–150 nm), microvesicles (100–1000 nm) and apoptotic bodies (< 1000 nm).

This review focuses on the role of exosomes as cell-to-cell communication in their functions during physiological and pathological processes, as well as potential biomarkers and therapeutic molecules of neuroinflammatory and neurodegenerative diseases. It also discusses the role of astroglial EVs in neuroinflammation in association with alcohol intake.

Biogenesis of Exosomes
The biogenesis of exosomes is a complex multistep process that initiates during the endocytosis process. This includes an initial invagination of the cell membrane in which encapsulating membrane and cytosolic elements lead to the formation of early endosomes, followed by their maturation to late endosomes to form multivesicular bodies. During this process, the endosomal membrane invaginates to generate intraluminal vesicles in the lumen of organelles (Hessvik and Llorente, 2018). Multivesicular body content can be transported to the lysosome complex where it is degraded or be reserved as temporary storage inside the cell or translocated to the plasma membrane, where multivesicular bodies fuse with it by pouring intraluminal vesicles (now exosomes) into the extracellular space (Hessvik and Llorente, 2018). Several molecules have been implicated in exosome biogenesis and release depending on either cell type or cellular homeostasis. However, the mechanisms involved in these processes are still not well understood (Hessvik and Llorente, 2018).

EVs, including exosomes, are highly enriched in tetraspanins, a family of proteins located in the clusters within membrane microdomains that interact with a variety of transmembrane and cytosolic signaling proteins. Tetraspanins are involved in the recycling routes between plasma membrane and several cellular organelles, and they regulate the biosynthetic maturation and trafficking of their associated partners (Andreu and Yáñez-Mó, 2014). By a proteomic analysis, it has been shown that tetraspanins CD9, CD63, CD37, CD81 or CD82 are mainly located in exosomal membranes. However, CD9, the first to be identified in exosomes, and CD63 and CD81, are the most frequently identified

proteins in exosomes and are considered classic markers of exosomes (Andreu and Yáñez-Mó, 2014).

Physiological Functions of Exosomes in Neuron-Glia Communication

It was first discovered that exosomes are assigned the function of removing unnecessary proteins and are known as the "garbage bins of the cell" (Rashed et al., 2017). However, recent evidence proves that exosomes can be involved in several physiological and pathological events. This duality occurs because exosomes perform a diverse range of functions and sometimes have opposing effects on recipient cells depending on the cell of origin and the physiological status of that cell upon exosome biogenesis. Under normal conditions, exosomes participate in many homeostatic processes, like apoptosis, angiogenesis, neurogenesis, wound healing, cell proliferation, inflammation, anti-inflammation and tissue maintenance, among others (Gupta and Pulliam, 2014).

One of the tissues that requires excellent fine control is the central nervous system (CNS). The exosomes secreted from the different neural cell types play critical roles during both CNS development and adult brain maintenance, including synaptic activity regulation and regeneration following injury. The interactions between glia-derived exosomes and neurons suggest a role of these vesicles in neural circuit development and maintenance by promoting neurite outgrowth from hippocampal neurons and increased cortical neurons survival (Caruso Bavisotto et al., 2019). During neuronal remodeling, the exosomes released by neurons are involved in synapse elimination and stimulate microglial phagocytosis. Neuronal exosomes also control complex coordinated communication with glial cells (Caruso Bavisotto et al., 2019). Among glial cells, astrocytes are involved in maintaining blood-brain barrier (BBB) integrity to synaptic regulation, and several lines of evidence show that lots of their functions are mediated by astrocyte-derived exosomes, which can promote neuroprotective properties to the neurons cultured under hypoxic conditions (Newman, 2003) (**Figure 1**). Astroglial cells also regulate extracellular glutamate levels and modulate synaptic activation. Neurons communicate with astrocytes by secreting exosomes containing several regulatory molecules that are internalized by astrocytes to, thus, elicit the neuronal-dependent modification of the expression of glutamate transporters (Morel et al., 2013; Vasile et al., 2017). Exosomes secreted by astroglial cells also transfer apolipoprotein D to neurons by mediating neuronal survival (Pascua-Maestro et al., 2018). These cells also express some innate immune receptors, such as Toll-like receptor (TLR)-4 and NOD-like receptor 3 (NLRP3), and they are capable of responding to tissue damage by releasing cytokines, chemokines and inflammatory mediators (Montesinos et al., 2016).

Microglia are the tissue-resident macrophages of the CNS and represent the first line of defense against pathogens. These cells are key players in immune regulation as they express immune receptors as TLRs, and they also produce soluble factors such as cytokines, chemokines, free radicals and reactive oxygen species, which mediate the inflammatory response. Microglia-derived EVs regulate synaptic transmission by promoting the neuronal production of ceramide and sphingosine to enhance excitatory neurotransmission *in vitro* and *in vivo*, which supports a physiological modulation of synaptic activity by microglia (Antonucci et al., 2012; Paolicelli et al., 2019) (**Figure 1**). These cells also produce immunomodulatory exosomes containing antigen-presentation molecules (MHC-I and MHC-II) and inflammatory-related miRNAs (e.g., mir-146a).

Finally, oligodendrocytes produce the myelin sheath to facilitate impulse conduction, while axonal integrity maintenance depends on support from oligodendrocytes (**Figure 1**). Recent studies demonstrate that the trophic function of these cells might well be related with exosomes from oligodendrocytes to neurons (Frühbeis et al., 2013; Lewis, 2013). Oligodendrocytes release exosomes containing myelin proteins, such as PLP, CNP, MAG, and MOG, as well as NAD-dependent deacetylase sirtuin-2, glycolytic enzymes and typical exosome-associated proteins (e.g., tetraspanins and heat-shock proteins). They also participate in bidirectional neuron–glia communication, contributing to neuronal activity and integrity. For instance, glutamate released by neurons in response to depolarization can trigger the activation of oligodendroglia glutamate receptors (N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). This stimulates the secretion of exosomes which, in turn, are internalized by neurons (Frühbeis et al., 2013). Moreover, in an *in vitro* cerebral ischemia model using neurons cultured under stressful growth conditions, exosomes from oligodendroglia protected these cells and promoted neuronal survival during oxygen-glucose deprivation (Fröhlich et al., 2014). These results indicate that oligodendroglial exosomes can influence neuronal physiology by regulating neuronal gene expression either by inducing distinct signaling pathways or by selective mRNA and miRNA transfer (Fröhlich et al., 2014).

These results support not only the critical role of exosomes in neuronal-glial communications, but also their role in the physiological functions in the CNS.

Role of Exosomes in Neuron-Glia Communication in the Context of Neuropathological Disorders

Exosomes are involved in the pathogenesis of many neuroinflammatory and neurodegenerative disorders (Gupta and Pulliam, 2014). Neuroinflammation is an innate immune response induced by microglia (the resident macrophages of the CNS) and astroglia, when they are activated by different types of insults or damage stimuli. Neuroinflammation leads to the production of cytokines, chemokines, reactive oxygen species and secondary messengers (Rama Rao and Kielian, 2015). Astrocyte-derived exosomes can also transport misfolded pathogenic proteins and/or aberrantly expressed miRNAs into neurons which then act to initiate or propagate neuroinflammation (Gupta and Pulliam, 2014), leading to

neural death and neurodegeneration (Wang et al., 2012). Glial cells can also shed exosomes loaded with pro-inflammatory molecules such as IL-1β (Bianco et al., 2005) and other cytokines involved in the promotion of neuroinflammation (**Figure 2**). Their scavenging functions are also crucial in the clearance of toxic compounds (Yuyama et al., 2012). Furthermore, endocrine signals from hematopoietic cells directed to the brain can be transported by glial exosomes, a phenomenon that is augmented in a context of inflammation (Ridder et al., 2014). It is interesting to note that extracellular vesicles can readily cross the BBB, adding a communication channel by which systemic inflammation can modulate physiological processes in the CNS.

Exosomes also contain miRNAs that can dysregulate the gene expression of neighboring cells. For instance, in a human cell line with similar overall levels of tau protein as those found in the postmortem brains of patients who had Alzheimer's disease, the exosomes containing proapoptotic proteins (e.g., prostate apoptosis response 4 and ceramide) and tau proteins are released by the astrocytes transferring these proteins to recipient cells to induce neural cell death and neurodegeneration (Reilly et al., 2017). *In vitro* and *in vivo* experiments also confirm that exosomes from neuronal cells contain precursors of amyloidogenic proteins and enzymes for the maturation of precursors (Pluta et al., 2018). In Parkinson's disease, using a transgenic mouse model expressing human α-synuclein, neuronal exosomes are involved in transporting toxic oligomers of α-synuclein to the extracellular environment by spreading this protein to healthy neurons and astrocytes which, in turn, induce an inflammatory response and cell death (Lee et al., 2010). In amyotrophic lateral sclerosis, in which mutations of copper/zinc superoxide dismutase 1 (SOD1) impair motor neuron viability, neurons and astrocytes are capable of secreting exosomes containing mutant SOD1 to the extracellular space by propagating the misfolding of SOD1 in human and murine cell models, which can induce motor neuron damage (Basso et al., 2013; Grad et al., 2014).

The concomitant transfer of antigens from oligodendrocytes to microglia is also implicated in the pathogenesis of autoimmune CNS diseases (Caruso Bavisotto et al., 2019). For instance, in an experimental mouse model of autoimmune encephalomyelitis, pro-inflammatory cytokines promote the release of exosomes by immune cells which, in turn, induce further pro-inflammatory molecules by spreading inflammation. The toxicity of glutamate accumulation also occurs in this disease, which triggers the release of exosomes by oligodendrocytes (Frühbeis et al., 2013), which could lead to demyelinated processes. Abnormalities in almost 100 miRNAs have also been found in several tissues of autoimmune diseases and multiple sclerosis. The overexpression of specific miRNAs in exosomes derived from serum samples of multiple sclerosis patients, reduces the frequency of immune cells by inhibiting naïve-cell differentiation and by playing a role in the pathogenesis of this disease (Ebrahimkhani et al., 2017).

Exosomes are also implicated in viral infections by participating in the initiation and progression of detrimental effects on neuronal viability. The neuronal loss that occurs in prion diseases is associated with the accumulation of the misfolded prion protein in neurons, and is enhanced by exosomes containing specific miRNAs (mir-29b, mir-128a and mir-146a) of murine infected neuronal cells that participate in neuronal dysfunction by dysregulating important genes (Bellingham et al., 2012). HIV infectious diseases are usually associated with neurological impairments, and in primary rat astrocyte cultures, drug abuse (e.g., opiates) during infection induces the release of exosomes enriched in mir-29b which could lead to neuronal impairment (Hu et al., 2012).

Different studies demonstrate that by activating the innate immune receptor TLR4, alcohol abuse induces neuroinflammation and neurodegeneration (Alfonso-Loeches et al., 2010, 2012). Recent studies in mouse astroglial cells demonstrate that ethanol increases the release of astrocyte-derived EVs and their content to inflammation-related proteins (e.g., NFκB-p65, NLRP3, caspase-1, IL-1β) and miRNAs (mir-146a, mir-182, and mir-200b) in a TLR4-dependent manner. Astrocyte-derived EVs can internalized by naïve cortical neurons to increase the neuronal levels of inflammatory protein (cyclooxygenase 2) and miRNAs (e.g., mir-146a) by triggering neuronal apoptotic cell death. The functional analysis of miRNAs has revealed the regulatory role of the miRNAs expressed in some genes involved in several inflammatory pathways. These events suggest that glial EVs might initiate and amplify the neuronal inflammatory response by leading to neuronal dysfunction and brain damage (Ibáñez et al., 2019) (**Figure 2**).

Interestingly, the involvement of exosomes in neuroinflammation has also been documented in mental disorders. For instance, chronic neuroinflammation is associated with certain forms of psychopathology, particularly depression (Saeedi et al., 2019). In several mental disorders (e.g., depression, anxiety, bipolar disorder and schizophrenia), a dysregulation occurs in the serotonin pathways that alters the release of microglial exosomes (Saeedi et al., 2019). The same study further demonstrated that the EVs isolated from the serum of patients with autism spectrum disorder are able to stimulate cultured human microglial cells to secrete more pro-inflammatory cytokines, such as IL-1β (Tsilioni and Theoharides, 2018).

In short, recent evidence supports the role of neural-derived exosomes, as active players in spreading neuroinflammation in neurodegenerative and neurological disorders (Vogel et al., 2018). However, these small vesicles can be also used to design engineered-EVs for therapeutic purposes and, indeed, novel approaches are currently being developed to implement the therapeutic use of EVs.

Exosomes as Therapeutic Agents and Biomarkers

Emerging evidence also indicates the potential role of exosomes as vectors containing miRNA, siRNA, mRNA, lncRNA, peptides, and synthetic drugs for cell therapy against

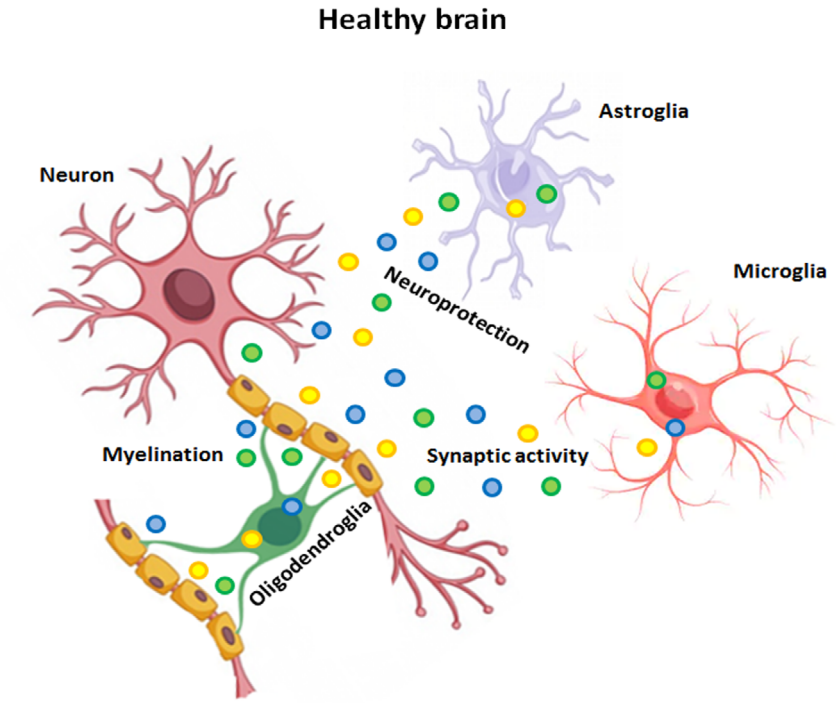

Figure 1 Roles of exosomes in the healthy brain.
Under physiological conditions, glial-derived exosomes mediate important functions participating in neural circuit development and maintenance, promoting neurite outgrowth, synaptic activity and neuronal survival. Oligodendrocytes-derived exosomes provide trophic support to axons facilitating myelination.

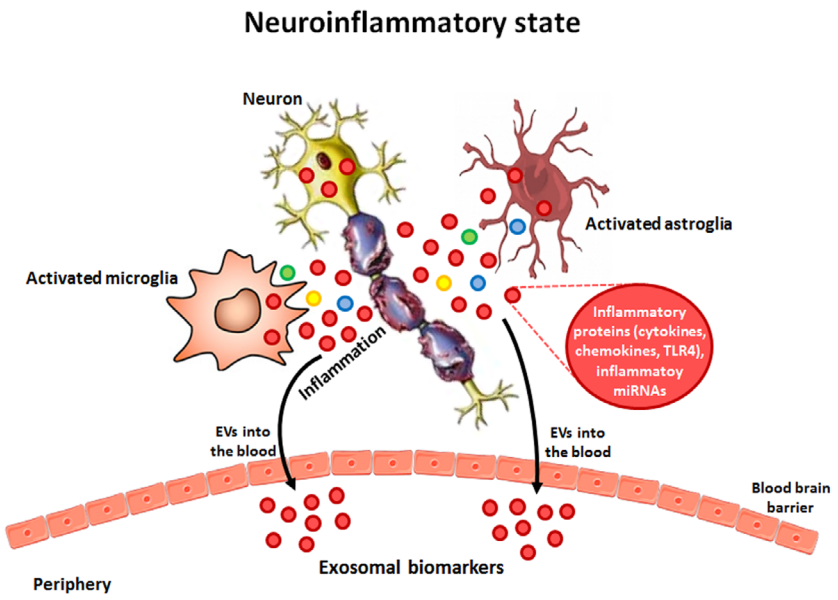

Figure 2 Roles of exosomes in a neuroinflammatory state.
After a neural insult, astroglial and microglial cells are activated and release exosomes which contain misfolded and inflammatory proteins and miRNAs involved in a neuroinflammatory response affecting the viability of the neurons. These exosomes are able to cross the blood brain barrier propagating the neuroinflammatory response to the periphery, and these peripheral exosomes can be used as potential biomarkers to the pathogenesis of neuroinflammation and neurodegenerative disorders. EVs: Extracellular vesicles.

neurological, neuroinflammatory and neurodegenerative diseases, as well as biomarkers to monitor brain diseases.

Exosomes have specific characteristics that make them the ideal way to therapeutically delivery molecules. For instance, exosomes have an intrinsic long-term circulatory capability as they are able to cross cell membranes and the BBB by transferring brain antigens to the periphery and regulating the peripheral immune system (de Rivero Vaccari et al., 2016) (**Figure 2**). These characteristics render exosomes potential candidates for delivering selected molecules as therapeutic drugs to specific target tissues. Early preclinical studies in exosomes delivery have shown that exosomes loaded with curcumin, a naturally anti-inflammatory polyphenol, not only increases the bioavailability and stability of the compound *in vivo*, but also significantly improves survival in lipopolysaccharide-induced septicemia (Zhuang et al., 2011). Brain inflammation in mice can also be ameliorated by intranasally administering curcumin-loaded exosomes (Zhuang et al., 2011). More recently, the use of exosomes as a therapy to alleviate some neurological disorders has been demonstrated in several studies. For instance, administering exosomes from mesenchymal stem cells mitigates some effects associated with traumatic brain injury or focal cerebral ischemia in animal models by increasing neurovascular re-

modeling and improving neurological, behavioral and cognitive outcomes during recovery (Zhang et al., 2019). Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorated cognitive decline in a mouse model of Alzheimer's disease by rescuing synaptic dysfunction, modulating astrocytic and microglial activity and decreasing pro-inflammatory factors such as TNF-α and IL-1β (Cui et al., 2018). Mesenchymal stem cell-derived exosomes also promoted neurogenesis and the recovery of cognitive function in Alzheimer's disease mouse models (Reza-Zaldivar et al., 2019).

Exosomes can also be manipulated *ex vivo* to carry therapeutic drugs or short interfering RNAs targeted against specific genes or miRNAs to modulate recovery, as demonstrated after stroke and traumatic brain injury in animal models. Indeed, clinical trials of exosomes as therapeutics are now underway in various diseases, including traumatic brain injury (Zhang et al., 2019).

Researchers have attempted to improve the targeting of exosomes to a specific type of cells or tissue in their therapeutic applications. Although blood-delivered exosomes usually accumulate in liver, kidney and spleen, exosomes may have target specific organs by the presence of different cell-binding receptor proteins or integrins on their surface (Liu and Su, 2019). Targeting exosomes can also be acquired by constructing antibody fragments or peptides on their surface, which can recognize antigens on recipient cells (Liu and Su, 2019). As these systems may affect the protein composition of exosomes and their function, new strategies are necessary to minimize changes in their composition. For instance, the use of micelles mixed with the EVs that derive from Neuro2A or platelet cells avoids EV size distribution, protein composition or morphology by improving cell specificity and prolonged circulation time (Kooijmans et al., 2016).

The fact that exosomes can cross the BBB and that their content is influenced by their cellular environment, has recently generated a lot of interest in their use as potential brain disorder biomarkers. The use of biomarkers could allow information about tissues otherwise inaccessible through direct examination and activated cell types to be obtained and may even be able to provide data about the nature of cellular activations (**Figure 2**). Nevertheless, the use of EVs/exosomes as neuropathology biomarkers has some limitations because they are present in low concentrations in peripheral biological fluids (e.g., blood, plasma or serum) which makes their detection difficult via currently available technologies. Therefore, although promising, the detection of glial EVs in the CSF may remain a non-specific parameter which will be helpful but not decisive in making diagnoses. However, recent studies have shown that exosomal miRNAs were differentially expressed in the postmortem prefrontal cortices of patients who had been diagnosed with schizophrenia or bipolar disorders compared to matched controls (Banigan et al., 2013). Likewise, a tumor-specific EGFR (epidermal growth factor receptor) transcript variant was detected in vesicles isolated from cancer patients and was considered a good biomarker candidate (Skog et al., 2008).

A recent study also demonstrated that plasma neuron-derived exosomes from HIV-infected participants with neuropsychological impairments present higher levels of high-mobility group box 1, neurofilament light polypeptide and amyloid-β proteins compared with neuropsychologically normal individuals (Sun et al., 2017). Likewise, the inflammation-induced circulating EVs that derive from endothelial cells mediate the acute phase response and sickness behavior associated with CNS inflammation, which demonstrates that EVs are capable of modifying behavioral responses (Couch et al., 2017).

Concluding Remarks

This review provides evidence to indicate the involvement of exosomes in neuron-glia communication and their participation in the different processes involved in the healthy and damaged brain. Under toxic or neuropathological stimulus (e.g., alcohol drug abuse) glial exosomes containing inflammatory molecules, such as pro-inflammatory cytokines, TLR4, RNAs and miRNAs, are able to communicate with neurons contributing to the pathogenesis of neuroinflammation and neurodegenerative disorders. Although new evidence demonstrated the importance of EVs/exosomes as therapeutic agents and as biomarkers of disease, further studies are needed to demonstrate the use of these nanoparticles for the detection of brain injury as well as to develop specific technologies capable to increase the performances of currently available assays.

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