Review Article

Exosomes in Neurologic and Psychiatric Disorders

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ABSTRACT

Purposes: The purposes of this review were to discuss the role of exosomes in neurologic and psychiatric diseases and to propose future therapeutic approaches.

Methods: PubMed was searched (2000–2014) using the terms *exosomes*, *microvesicles*, *neurological disorders*, *psychiatric disorders*, *multivesicular bodies*, *Alzheimer's disease*, *Parkinson's disease*, *prion disease*, *multiple sclerosis*, *schizophrenia*, *glioblastoma multiforme*, and *flavonoids*.

Findings: Many cells of the nervous system have been reported to release exosomes that could have an active role in the function, development, and diseases of the CNS, such as Alzheimer disease, Parkinson disease, prion diseases, multiple sclerosis, brain tumors, and schizophrenia. In all of these diseases, exosomes are involved in the spread of "toxic" proteins that are mutated or "misfolded" and serve as templates for the formation of disease-producing oligomers.

Implications: Exosomes' simple structure and abilities to be incorporated into plasma membrane and to cross the blood–brain barrier allow for the opportunity to utilize them as delivery vehicles of drugs and genetic elements in the treatment of immune, psychiatric, and neurologic disorders. Flavonoids have emerged as unique, natural molecules with antioxidant and antiinflammatory properties. It would, therefore, be of interest to design flavonoid-containing exosomes. (*Clin Ther*. 2014;36:882–888)

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Key words: exosomes, flavonoids, neurological disorders, psychiatric disorders.

INTRODUCTION

Exosomes are small membrane vesicles secreted by diverse cell types (eg, neurons, tumor cells, and kidney cells).[1] They are secreted in the intercellular space but can be isolated from various biological fluids, such as plasma, urine, cerebrospinal fluid, epididymal fluid, amniotic fluid, malignant and pleural effusions of ascites, bronchoalveolar lavage fluid, synovial fluid, and breast milk, suggesting a role in the exchange of biological

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information across distant bodily compartments.[2] Exosomes are either generated from the cell when multivesicular bodies (MVBs) fuse with the plasma membranes, or they are released directly from the plasma membrane.[3] Exosomes secreted in bodily fluids contain a variety of proteins, lipids, noncoding RNAs, mRNAs, and microRNAs (miRNAs) that are delivered to the surrounding cells or are carried to distal sites.[4,5]

The role that exosomes may play in the central nervous system (CNS) is the subject of active investigation.[6] Many cells of the nervous system have been reported to release exosomes that may have an active role in the function, development, and diseases of the CNS.[7] Interestingly, exosomes have been found to be associated with several proteins, such as amyloid precursor protein and α-synuclein, which appear to be involved in Alzheimer disease (AD) and Parkinson disease (PD), respectively.[8] Recent findings have also implied an unexpected role of exosomes, and their mode of membrane exchange, in the transmission of a pathogen called the *prion,* which is involved in Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy (scrapie).[9]

Based on these findings, exosomes comprise a source of multiple markers that provide clinically useful information. The purposes of this review were to discuss the role of exosomes in neurologic and psychiatric diseases and to propose future therapeutic approaches.

MATERIALS AND METHODS

PubMed was searched for relevant articles published from 2000 to 2014 using the terms *exosomes, microvesicles, neurological disorders, psychiatric disorders, multivesicular bodies, Alzheimer's disease, Parkinson's disease, prion disease, multiple sclerosis, schizophrenia, glioblastoma multiforme,* and *flavonoids*.

RESULTS

The literature search identified 71 articles relevant to the present review.

Neurodegeneration and Exosomes

Extracellular membrane vesicles may be involved in the spread of toxic proteins within the nervous system in a number of neurologic diseases, such as AD, PD, prion diseases, multiple sclerosis (MS), brain tumor, and schizophrenia (SZ).[10–15] In all of these diseases, exosomes are involved in the spread of "toxic" proteins that are mutated or "misfolded" and serve as templates for the formation of disease-producing oligomers.[10,16] Neurons may try to dispose of these proteins by processing them through the endosomal pathway, which leads either to degradation into lysosomes or to incorporation into MVBs and release into the extracellular space as exosomes.

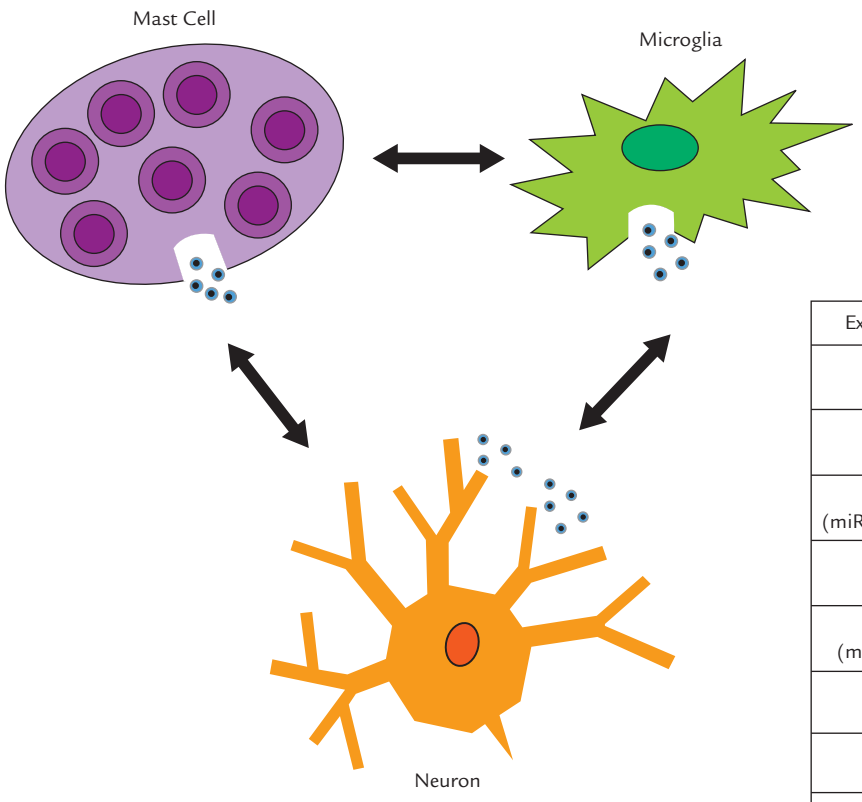
Alzheimer's Disease

AD is a late-onset neurologic disorder with progressive loss of memory and cognitive ability as a result of neuronal impairment and death. AD is characterized pathologically by extensive extraneuronal deposition of amyloid-β (Aβ) fibrils in the brain as amyloidal plaques and by impairment of synaptic plasticity.[17] The main component of amyloid is polymerized Aβ peptide, a 39 to 43–amino acid residue peptide produced by proteolytic cleavage from the amyloid precursor protein.[18] However, all trials aimed at minimizing the burden of Aβ deposition have failed to produce any significant benefit.[19–22] Instead, recent work indicates focal brain inflammation as the key pathologic process involved.[23]

There is increasing evidence that exosomes may participate in the progression of AD. In a recent report, Aβ processing was associated with endosomal compartments, with a fraction of Aβ and C-terminal fragments being secreted in association with exosomes.[24] In addition, it was reported that activated primary cultured astrocytes release proapoptotic exosomes in response to challenge with Aβ.[25] Exosomes from neuroblastoma 2a and microglial cell line BV-2 cells have also been reported to promote the extracellular enzymatic degradation of Aβ.[26] Furthermore, neuron-derived exosomes have been reported to promote Aβ fibrilization and degradation by the microglia.[8] Moreover, upregulation of exosome secretion by the specific sphingolipid-metabolizing enzyme sphingomyelinase 2 has been reported as sufficient for inducing the enhancement of Aβ uptake by microglia.[8] Therefore, in addition to blocking exosome-mediated plaque formation, inhibition of sphingomyelinase 2 may reduce the neuroinflammation that occurs during AD progression, as well as prevent apoptosis of neurons and astrocytes.[27]

Parkinson Disease

PD is the second most common neurodegenerative disease after AD and is characterized by selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies primarily composed of fibrillar α-synuclein and ubiquitineted



Exosome Molecule	Disease
DNA	Pancreatic Cancer
RNA (RNU6-1)	GBM
miRNA (miR-320, miR-576-3p)	GBM
miRNA (miR-497)	SZ
miRNA (miR-219, miR-122)	MS
APP	Alzheimer's disease
α-syn, LRRK2	Parkinson's disease
PrP^{c} PrP^{sc}	Prion diseases

Figure. Cross-talk among brain mast cell, microglia and neurons through exosomes. The box indicates the most common molecules contained in exosomes and diseases with which they have been associated. α-syn = α-synuclein; APP = amyloid precursor protein; LRRK = leucine-rich receptor kinase; miR, miRNA = microRNA; PRP^{c} = cellular form of the prion protein; PrP^{sc} = scrapie isoform of PRP^{c}; RNU6-1 = nuclear RNA 6-1.

proteins in the surviving neurons.[28] Ninety percent of cases of PD are sporadic, but familial cases have been associated with different genes.

Recent studies have provided strong evidence that the leucine-rich receptor kinase (LRRK) 2 plays an important role in exosome secretion and in the fusion of MVBs with the plasma membrane.[29] LRRK2 has been reported to interact with Rab5b, a member of the Ras proto-oncogene family and a regulator of endocytic vesicle trafficking.[30] In addition, the *R1441C* mutation on *LRRK2* induces the formation of skeinlike abnormal MVBs.[29] Under pathologic conditions, τ protein, which is involved in the pathogenesis of AD, can accelerate exosome-mediated release containing α-synuclein toxic forms from injured neurons because it can interact with α-synuclein, promoting the oligomerization and the toxicity of these proteins.[31] Neurons with a defective retromere complex, which performs retrograde transport from an endosome to the Golgi apparatus, have increased exosomal secretion of amyloid precursor protein.[32] In a recent study, α-synuclein was reported to stimulate exosome secretion by murine microglial BV-2 cells. These exosomes expressed a high level of major histocompatibility complex class II molecules and membrane tumor necrosis factor-α and caused increased apoptosis.[33]

Multiple Sclerosis

MS is a chronic autoimmune disease affecting the CNS the cause of which remains unclear. However, it has been established that the pathogenesis of the disease is linked to a variety of genetic, environmental, stress, and immunologic factors.[34,35]

Much of the current research on exosomes has focused on the utility of extracellular miRNAs, such

as miR-122, which is currently identified as associated exclusively with MS.[36] A recent study reported that serum exosomes produced by young or environmental enrichment–exposed rats had significantly increased myelin content, oligodendrocyte precursor cell levels and neural stem cell levels, and reduced oxidative stress in hippocampal slice cultures.[37] Exposure of aged animals to environmental enrichment was reported to have restored the animals' ability to produce these myelination-promoting exosomes. These exosomes contain high levels of miR-219, which plays a role in the formation and maintenance of compact myelin[38,39] and is deficient in humans with MS.[40] In addition, exosomes produced by interferon-γ–stimulated dendritic cells have been reported to increase myelination and oxidative stress tolerance in vitro and in vivo. These interferon-γ–stimulated dendritic cell–derived exosomes also contain high levels of miR-219.[41] Stimulated dendritic cell exosomes contain high levels of specific antiinflammatory miRNAs that may serve an immunomodulatory role in suppressing the development of MS.

Prion Diseases

Prion diseases are fatal, transmissible, neurodegenerative disorders that include Creutzfeldt-Jakob disease and Gerstmann-Sträussler-Scheinker syndrome in humans, bovine spongiform encephalopathy, and scrapie in sheep.[9] The major component of the infectious prion agent is an abnormal isoform of the cellular form of the prion protein (PrP^{C}) referred to as PrP^{Sc} and leads to neuronal death, causing large spongiform vacuoles in brain tissue.[42]

Both PrP^{C} and PrP^{Sc} forms have been associated with exosomes, and PrP^{Sc}-containing exosomes have been reported as infectious in both animals and cell bioassays.[10,43] Except for the studies that used cell cultures to isolate the exosomal vesicles, primarily cultured neurons and cerebrospinal fluid have been used as sources of exosomes in which PrP^{C} has been detected.[10,44] PrP^{C} is tethered to the plasma membrane by a glycosylphosphatidylinositol anchor, and the conversion of PrP^{C} to PrP^{Sc} has been suggested to occur in lipid raft regions.[45] The presence of lipid rafts in exosomes could also aid in its ability to transmit PrP^{Sc}.[46]

Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most common and most aggressive malignant primary brain tumor in adults. Despite recent advances in treatment, the prognosis of patients with this disease remains discouraging, with median overall survival times of <15 months.[47,48]

A recent study reported that exosomes from GBM cells are enriched with RNAs associated with proliferation, invasion, and immune repression.[49] Exosomes could constitute a potent mediator of hypoxia-dependent communication between malignant and vascular cells, suggesting an important role of exosomes in hypoxia-driven GBM development.[50] Thus, exosomes may serve as a noninvasive biomarker for assessing the oxygenation status and aggressiveness of malignant tumors. Recent studies have reported that a small, noncoding RNA signature of 2 miRNAs (miR-320 and miR-574-3p) and 1 small nuclear RNA (RNU6-1) found in exosomes isolated from the serum of GBM patients could serve as a potential diagnostic biomarker.[47] Therapeutic miRNA produced in marrow stromal cells and loaded into extracellular exosomes has been suggested as a new treatment of malignant glioma.[51]

Schizophrenia

SZ is a neuropsychiatric disorder characterized by behavioral and cognitive deficits, as well as impaired locomotor activity. The diagnosis of SZ is associated with demonstrable alterations in brain structure and changes in dopamine and glutamate neurotransmission in the cortex.[52]

A recent study reported that certain exosomal miRNAs from frozen postmortem brain samples of prefrontal cortex were differentially expressed in patients with SZ or bipolar disorder compared with controls. Specifically, 2 exosome-derived miRNAs, miR-497 in SZ samples and miR-29c in bipolar disorder samples, were significantly increased compared with those in control samples.[11]

DISCUSSION

Exosomes may represent the future of biomarkers in medicine because they may contain disease biomarkers or they may be the vectors for a variety of molecules, including protein and nucleic acids. This theranostic approach has potential in the field of personalized medicine because it allows for targeting the diseased areas in individual patients, possibly at early clinical stages. Increasing evidence indicates that brain inflammation contributes to the pathogenesis of many

neuroimmune and neuropsychiatric disorders.[53–55] Flavonoids have emerged as unique natural molecules with antioxidant and antiinflammatory properties.[56] They can inhibit mast cell[57] and microglial cell[58] activation, which are uniquely important because mast cell–microglia interaction is a crucial process in brain pathophysiology (**Figure**).[59] Moreover, flavonoids have been shown to be beneficial in MS and to inhibit autoimmune T cells.[60–63] It is of interest that exosomes can also deliver suppressor T cell microRNAs that can inhibit effector T cells.[64] It would, therefore, be of interest to design flavonoid-containing exosomes.

CONCLUSIONS

The function of exosomes appears to be much more than just a secretory mechanism of cellular contents. It is a sophisticated means of processing specific molecules, and the versatile role of exosomes opens up new perspectives for the understanding and treatment of neurologic diseases. Further studies are needed to evaluate the potential of exosome-derived miRNAs as biomarkers for diseases. Furthermore, the rapid development of exosome nanotechnology may add alternative-therapeutics delivery to the emerging diagnostic potential of brain-derived exosomes in neuropsychiatric diseases.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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