REVIEW

Exosomes: a novel therapeutic target for Alzheimer's disease?

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Abstract
Extracellular exosomes are formed inside the cytoplasm of cells in compartments known as multivesicular bodies. Thus, exosomes contain cytoplasmic content. Multivesicular bodies fuse with the plasma membrane and release exosomes into the extracellular environment. Comprehensive research suggests that exosomes act as both inflammatory intermediaries and critical inducers of oxidative stress to drive progression of Alzheimer's disease. An important role of exosomes in Alzheimer's disease includes the formation of neurofibrillary tangles and beta-amyloid production, clearance, and accumulation. In addition, exosomes are involved in neuroinflammation and oxidative stress, which both act as triggers for beta-amyloid pathogenesis and tau hyperphosphorylation. Further, it has been shown that exosomes are strongly associated with beta-amyloid clearance. Thus, effective measures for regulating exosome metabolism may be novel drug targets for Alzheimer's disease.

Key Words: *nerve regeneration; microvesicle; beta-amyloid; tau; neuroinflammation; oxidative stress; therapeutic target; neurodegeneration; dementia; neural regeneration*

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Introduction
Alzheimer's disease (AD) is the most common cause of dementia, and an age-related neurodegenerative disease characterized by progressive memory loss and declining cognitive function. Multiple pathogenic hypotheses have been proposed including amyloid, extracellular beta-amyloid (Aβ) peptide deposition (Lloret et al., 2011; Busche et al., 2016), intracellular accumulation of hyperphosphorylated tau protein (formation of neurofibrillary tangles) (Lloret et al., 2011; Busche et al., 2016; Panza et al., 2016), cholinergic dysfunction (Picon et al., 2010; Cacabelos et al., 2014), neuroinflammation, and oxidative stress (Latta et al., 2015; Liu et al., 2015). Although several medications are available to treat AD, none of them stop or reverse the disease (de la Torre, 2010). Increased knowledge on available treatments and the existing pathogenesis of AD will be beneficial for reaching the best decisions on medications and preventing progression of AD.

Apart from macromolecular complexes and small molecules, a large number of microvesicles are secreted from cells into the extracellular space (Vlassov et al., 2012; Beach et al., 2014). Microvesicles (also known as circulating microvesicles or microparticles) are fragments of plasma membrane between 100 nm and 1,000 nm in diameter. Exosomes are microvesicles secreted by all cells. Exosomes first fuse with multivesicular bodies (MVBs) and the cell surface, and are subsequently released from MVBs into the extracellular space (Laulagnier et al., 2004; Vlassov et al., 2012). MVBs are referred to as late endosomes and contain internal vesicles. The most important role of exosomes is to act as intercellular communication messengers by delivering macromolecules between cells (Thery et al., 2002; Beach et al., 2014). Substantial evidence suggests that exosomes serve as active mediators of neurodegenerative disorders, and transport disease particles such as α-synuclein (Chang et al., 2013; Kong et al., 2014; Tsunemi et al., 2014; Grey et al., 2015), Aβ, and prions from their cells of origin to other cells (Kalani et al., 2014; Yuyama et al., 2014; Fiandaca et al., 2015; Yuyama et al., 2015). This review discusses the role of exosomes in the pathogenesis of AD, and addresses the association between exosomes and relevant AD pathologies (Aβ, neurofibrillary tangles, oxidative stress, and inflammation). Moreover, this review provides a proposed general role of exosomes in AD pathogenesis, and discusses novel therapeutic interventions of exosomes for AD.

Exosomes
Exosomes are microvesicles of 30–100 nm in diameter, and small lipid vesicles secreted by all cell types (Kastelowitz and Yin, 2014; Sluijter et al., 2014). Internal vesicles formed by the inward budding of cellular compartments are known as MVBs (Vlassov et al., 2012; Al-Nedawi, 2014). When MVBs fuse with the plasma membrane, exosomes are released from these internal vesicles. Exosomes exist in blood, saliva, urine, breast milk, and other body fluids (Vlassov et al., 2012; Qin and Xu, 2014). Exosomes not only maintain normal cellular functions and cellular viability *via* housekeeping roles, but also safeguard various functions of multicellular organisms (Ohno, 2006).

Exosomes contain various substances, including small RNAs, lipids, and a variety of proteins (Vitek et al., 1994; Beach et al., 2014). MicroRNAs (miRNAs) target messenger RNAs for degradation and prevent translation. It has been shown that exosome-released miRNAs regulate the inflam-

matory response to external environmental changes. For example, exosome-delivered miR-155 increases expression of inflammatory genes, while miR-146a decreases their expression (Gao et al., 2016). The most intriguing role of exosomes are as conveyors of proteins and lipids, which affect downstream signaling events in recipient cells and influence various aspects of cell behavior and physiology, including nerve regeneration, and synaptic function and behavior (Arscott et al., 2013; Chen et al., 2014). Exosomes may serve as vesicular carriers for intercellular communication in neurodegenerative disorders (Schneider and Simons, 2013). Further, they play an ominous role in propagation of toxic Aβ pathology (enhancing Aβ generation and deposition, and inhibiting Aβ clearance), abnormal tau phosphorylation, and triggering neuroinflammation and oxidative stress by exchange of information between neurons and glia in neurodegenerative AD conditions (Saman et al., 2014; Yuyama et al., 2014, 2015; Fiandaca et al., 2015; Goetzl et al., 2016; Shi et al., 2016).

Exosomes and Neurodegeneration

Neurodegeneration encompasses a series of diseases due to loss of structure and function of nerve cells in the brain. Most attention has been focused on Parkinson's disease (PD), Huntington's disease, and AD (Tonekaboni and Mollamohammadi, 2014; Mouton-Liger et al., 2015). Indeed, a large proportion of less popular diseases have been ignored (Kerner, 2014), such as multiple sclerosis (Orack et al., 2015), epilepsy (Aboud et al., 2013; Pottoo et al., 2014), and stroke (Seifert et al., 2014; Walberer et al., 2014). Increasing evidence indicates that exosomes are involved in neurodegenerative disorders as potential carriers of misfolded proteins (Russo et al., 2012; Candelario and Steindler, 2014; Kalani et al., 2014).

Two of the most common neurodegenerative diseases are AD and PD. The main cause of PD is death of dopaminergic cells in the substantia nigra. Emerging studies have shown that progression of neurodegeneration in PD may involve release of toxic forms of α-synuclein, which are taken up by neighboring neurons and trigger dysfunction (Russo et al., 2012). Several studies have noted that exosomes are involved in PD pathogenesis such as acceleration of α-synuclein aggregation (Tsunemi et al., 2014; Grey et al., 2015). Molecular biology data support the proposition that lysosomal dysfunction leads to increased α-synuclein release in exosomes, and a concomitant increase in α-synuclein transmission to recipient cells (Alvarez-Erviti et al., 2011). Additionally, an *in vitro* study suggested involvement of ATP13A2/(PARK9) in exosome biogenesis and α-synuclein secretion (Tsunemi et al., 2014). While PD-linked human ATP13A2/(PARK9) promotes α-synuclein externalization *via* exosomes (Kong et al., 2014). Furthermore, exosomes secreted from activated microglia are important mediators of α-synuclein-induced neurodegeneration (Chang et al., 2013).

Exosomes and Amyloid Pathology

Senile plaques produced by accumulation of Aβ are a classical hallmark of AD. Aβ originates from sequential cleavage of amyloid precursor protein (APP) (Tam et al., 2014; Agostinho et al., 2015). Cleavage by β-secretase within the luminal/extracellular domain leads to generation of β-carboxyl-terminal fragments (CTFs) (Cai et al., 2012; Ortega et al., 2013). Following β-secretase cleavage, γ-secretase processes APP at the carboxyl-terminus to produce Aβ. CTFs of APP can accumulate in MVBs and be released from the cell in exosomes (Sharples et al., 2008). Exosomes also contain CTFs and β- and γ-secretases (Sharples et al., 2008), indicating a wider role in APP metabolism.

Formation and clearance of Aβ are associated with endosomal compartments as Aβ and CTFs are secreted from exosomes (Rajendran et al., 2006). Cleavage of APP by β-secretase occurs in early endosomes (Rajendran et al., 2006). Exosome-associated Aβ levels increased more significantly in the cerebrospinal fluid of younger cynomolgus monkeys and APP transgenic mice compared with older animals (Yuyama et al., 2015). Additional evidence has confirmed that exosomes promote Aβ aggregation and accelerate amyloid plaque formation (Dinkins et al., 2014). Meanwhile, *in vivo* exosome reduction contributes to lower amyloid plaque load in the 5xFAD mouse model, a mouse line that expresses five mutations of familial AD (Dinkins et al., 2014).

Recent evidence revealed that infusion of neuronal exosomes into the brain of APP transgenic mice decreased Aβ generation and deposition, which was not observed with glial exosomes (Yuyama et al., 2015). This finding highlights the role of neuronal exosomes in Aβ clearance (Yuyama et al., 2015), and suggests that diminished secretion of neuronal exosomes may relate to Aβ accumulation, and ultimately, development of AD pathology (**Figure 1**). Indeed, it appears that improving Aβ clearance by exosome administration may provide a novel therapeutic intervention for AD (Yuyama et al., 2014).

Exosomes and Neurofibrillary Tangles

Neurofibrillary tangles are aggregates of hyperphosphorylated tau protein (Gendreau and Hall, 2013). Definitive diagnosis of AD requires postmortem identification of amyloid plaques and neurofibrillary tangles. Several studies suggest that tau can be secreted from neurons *via* exosomes, and exosome-related tau may be an important contributor to spreading neurofibrillary lesions (Vingtdeux et al., 2012; Saman et al., 2014).

Exosomes as a novel way of interneuronal communication, participate in spreading pathological proteins (such as APP fragments, phosphorylated tau, or α-synuclein) across the nervous system (Chivet et al., 2012, 2013). There is significant correlation between multiple genes of AD and proteins recruited to exosomes by tau overexpression (Saman et al., 2014). A clinical study showed that exosome levels of total tau (pT181-tau and pS396-tau) were significantly higher in AD patients than case-controls, both 1–10 years before and at AD diagnosis, suggesting that pS396-tau and pT181-tau levels in extracts of neutrally-derived blood exosomes predict AD development before clinical onset (Fiandaca et al., 2015). In addition, exosome-associated tau phosphorylated at Thr-181 (AT270) is present in human cerebrospinal fluid samples, suggesting that phosphorylated tau induced by exosome secretion may contribute to abnormal tau processing (Saman et al., 2012).

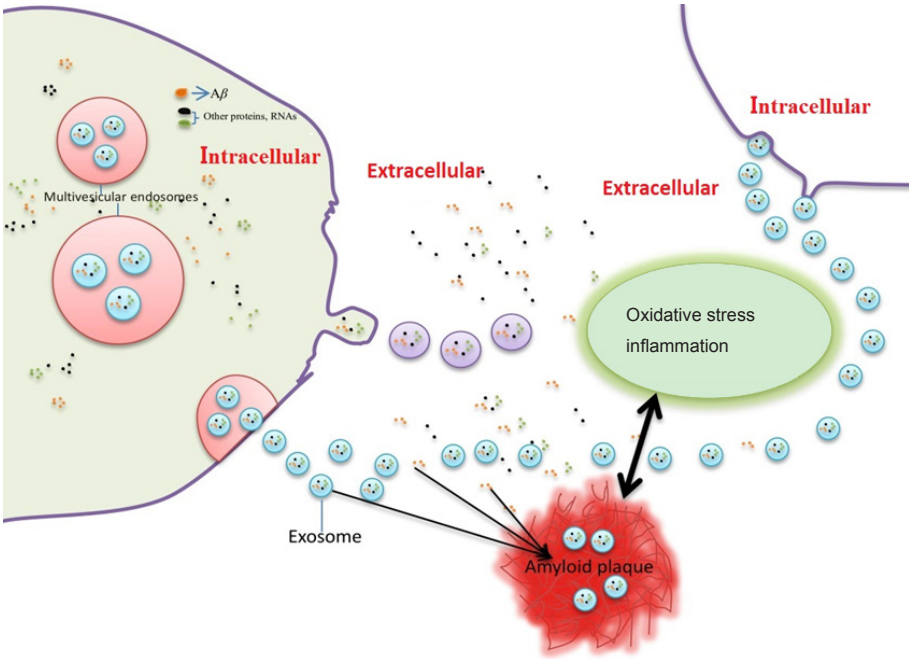

Figure 1 Schematic diagram of the emerging role of exosomes in beta-amyloid peptide pathology.
Exosomes are formed inside multivesicular bodies in cells. Exosomes are released into the extracellular environment when multivesicular bodies fuse with the plasma membrane. Beta-amyloid (Aβ) can be secreted from cells by association with exosomes. Aβ secreted from exosomes in the extracellular space contributes to Aβ plaque formation, which in turn triggers neuroinflammation and oxidative stress.

Exosomes as Mediators of Neuroinflammation Associated with AD

Inflammation represents a response induced by injury or destruction of tissues, which enables removal, dilution, or isolation of both injurious substances and injured tissue. Neuroinflammation is inflammation of nervous tissue, and is a pathological and physiological process in response to a variety of events (Cai et al., 2013a, 2014), including microbial infections (Cox et al., 2013), chemical substances (de Rivero Vaccari et al., 2016), tissue necrosis from ischemia and anoxia (Maddahi and Edvinsson, 2010), traumatic brain injury (Lozano et al., 2015; de Rivero Vaccari et al., 2016), toxic metabolites (Butterworth, 2011; McMillin et al., 2014), and autoimmunity (Liu et al., 2014; Morales et al., 2014). It is well known that inflammation can be classified as either acute or chronic. As a common inflammatory process, acute neuroinflammation occurs immediately following injury to the central nervous system. It is characterized by the release of inflammatory molecules, glial cell activation, endothelial cell activation, platelet deposition, and tissue edema. Meanwhile, chronic neuroinflammation is of longer duration, with maintained glial cell activation and recruitment of other immune cells in the brain (Millington et al., 2014; Phillips et al., 2014). Neuroinflammation is regarded as chronic inflammation of the central nervous system. Mounting evidence shows that AD is associated with chronic inflammatory responses, with sustained presence of inflammatory cytokines from activated microglia and astrocytes, free radicals, and oxidative stress (Kaur et al., 2015; Latta et al., 2015; Zhang and Jiang, 2015).

Exosomes are emerging as important inflammatory mediators because of their role as cargo of inflammatory molecules, and thereby induce neuroinflammation by exchange of information between neurons and glia (Gupta and Pulliam, 2014; Kore and Abraham, 2014; Rajendran et al., 2014; Fernandez-Messina et al., 2015; de Rivero Vaccari et al., 2016). Aβ is effectively packaged into exosomes and spread from one cell to another, initiating an inflammatory cascade (Gupta and Pulliam, 2014). In addition to releasing inflammatory factors, exosomes secreted by dead brain cells can influence bystander cells by the transfer of inflammatory mediators in response to pathogenic stimuli (Prado et al., 2010; Sun et al., 2010; Gupta and Pulliam, 2014). Extracellular exosomes release Aβ and accelerate amyloid plaque formation, which are important causes of neuroinflammation (Engel, 2014). Considering their ability to mediate intercellular communication between cells (Record, 2014; Salido-Guadarrama et al., 2014; Zhang and Grizzle, 2014), exosomes represent one of the key players in transporting neurotoxic inflammatory agents and spreading progression of inflammation in brain cells. Oversecretion of exosomes is harmful and can strengthen progression of inflammation in the extracellular microenvironment. Nonetheless, despite abundant evidence demonstrating a role for exosomes in regulating the inflammatory response, the exact mechanisms remain unclear. Therefore, improved understanding of the role of exosomes in inflammation at different stages of AD will benefit prevention and treatment of AD.

Oxidative Stress: A Direct Mediator of Exosome Release in AD?

Extensive research has shown that oxidative stress is strongly linked to AD pathogenesis (Cai et al., 2011, 2013b; Ferreira et al., 2015). An important feature of AD is an active and self-perpetuating cycle of chronic neuroinflammation and oxidative stress that may contribute to irreversible neuronal dysfunction and cell death (Cai, 2014). Oxidative stress is proposed to contribute to Aβ generation and formation of neurofibrillary tangles (Santos et al., 2014; Kanamaru et al., 2015; Kamat et al., 2016). Many results show that neuroinflammation-induced oxidative stress increases Aβ generation by enhancing β- and γ-secretase activity (Cai et al., 2011; Bonda et al., 2014; Chang et al., 2014). In addition, intracellular Aβ accumulation promotes significant oxidative and

inflammatory mechanisms that generate a vicious cycle of Aβ generation and oxidation, each accelerating the other (Luque-Contreras et al., 2014; Persson et al., 2014).

Many studies have noted that exosome release from MVBs are induced and accelerated by oxidative stress (Soderberg et al., 2007; Eldh et al., 2010; Zhou et al., 2013; Tsanova et al., 2014). Previous studies have indicated that exosome release from MVBs is associated with the pathogenesis of many diseases involved in oxidative stress (Tsanova et al., 2014), such as multiple sclerosis and dysmyelinating syndromes (Pusic et al., 2014), cancer (Goldkorn et al., 2013; Meseure et al., 2014), cerebral ischemia disease (DeGracia et al., 2008; Fröhlich et al., 2014), as well as cardiovascular disease (Fleury et al., 2014; Yamaguchi et al., 2015). However, many questions have not been answered: what is the exact role of exosome release mediated by oxidative damage in AD pathogenesis? Is release of exosomes from MVBs a cause or consequence of oxidative stress in AD? What is the relationship between oxidative-mediated release of exosomes and AD pathology?

Exosomes: A Novel Therapeutic Strategy for AD?

AD is a progressive brain disorder and the most common form of dementia. To date, there is still no cure for AD that can reverse or halt its progress, although there are medications that can help improve symptoms in some cases. Exosomes are extracellular vesicles that transport different molecules between cells. They are formed and stored inside MVBs until they are released to the extracellular environment. It is apparent that the brain microenvironment correlates with neurodegeneration, and brain intercellular communication induced by exosomes is necessary for this to occur. In the past decade, exosomes have been shown to be efficient carriers of genetic information, which can be transferred between cells to regulate gene expression and function of recipient cells (Fernandez-Messina et al., 2015). Hence, they may be an important means of regulating the neurodegenerative process underlying AD, and improve the brain microenvironment by affecting the intercellular communication induced by exosomes.

Exosomes can cross the blood-brain barrier and therefore be used as delivery vehicles of drugs and genetic elements for treatment of neurological disorders. Several studies have suggested that exosomes derived from multipluripotent mesenchymal stromal cells play a neuroprotective role by promoting functional recovery (Xin et al., 2014), neurovascular plasticity (Xin et al., 2013a, b; Zhang et al., 2015), and repairing injured tissue in traumatic brain injury and neurodegenerative disorders. Thus, it may be possible to use mesenchymal stromal cell exosomes in therapies for AD (Katsuda et al., 2015). Furthermore, intracerebrally administered exosomes can act as potent Aβ scavengers by binding to Aβ through enriched glycans on glycosphingolipids on the exosome surface, suggesting a role for exosomes in Aβ clearance in the central nervous system (Yuyama et al., 2014). Improving Aβ clearance by exosome administration provides a novel therapeutic intervention for AD.

Ambiguous knowledge of the underlying mechanisms responsible for causing AD and its progression is the major impediment to therapeutic advances. The potential role of exosomes in neurological disorders and knowledge of their biology show promising leads that are close to clinical translation. Regulating the status and state of exosomes may be a 'Trojan-horse' approach to deliver drugs into the brain and treat neurodegenerative and other disorders.

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