Effect of Exosomes on Alzheimer’s Disease

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Abstract

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by latent and progressive onset. At present, there is a lack of effective diagnosis and treatment of AD, and AD constitutes an exceptional burden on the lives of patients and their families. The study of exosomes has uncovered promising new possibilities for the diagnosis and treatment of AD. This commentary describes the role of exosomes in Alzheimer’s disease.

Keywords: Exosomes; Alzheimer’s disease; Urinary

AD is a neurodegenerative disease characterized by progressive cognitive impairment, behavioral changes, memory loss and executive dysfunction, all of which present serious threats to the health of older people [1]. It has been proposed that the pathology of AD spreads between functionally and anatomically connected brain regions through prion-like mechanisms [2-6], which promote the progression of neurological diseases. Methods for early diagnosis and treatment of AD are urgently needed in order to delay the progress of the disease and preserve the quality of life of patients.

After the fusion of multi-vesicle bodies (MVBs) and the plasma membrane, exosomes are released into the extracellular space [7]. When exosomes are absorbed by receptor cells, they transfer their contents [8], which can promote the transmission of pathological proteins between nerve cells and encourage the development of neurodegenerative diseases. Exocrine bodies are abundant in blood, saliva, urine, semen, amniotic fluid, ascites, cerebrospinal fluid (CSF) and breast milk [9]. There is growing evidence that exosomes freely cross the blood-brain barrier (BBB) [10-12], and it follows that exosomes in CSF can cross the blood-brain barrier to reach the blood and then pass through the kidneys into the urine. Given consistent control of other factors, such as age, region, education level, and no other related diseases, changes in the contents of plasma and urine exosomes can reflect changes in the brain to a certain extent.

Exosomes vary in size and shape depending on their origin and function [13], and they can be distinguished in clinical studies by transmission electron microscopy (TEM). Negative staining is considered to be the best method for TEM imaging of exocrine bodies [14], because it can detect most exosomes. Gradual technical advances in this method have made it possible to observe the detailed structure of exosomes [15].

Nanoparticle tracking analysis (NTA) is a method that was developed in recent years allowing quantitative measurement of the size of particles with diameters ranging from 30 nm to 1 μm. It can also be used to measure the diameter and number of exosomes. The NTA technology depends on the NanoSight instrument, which is equipped with a highly sensitive camera and a vertical microscope with a laser light source. The particle size distribution and particle number in the liquid suspension are obtained by using the characteristics of light scattering and Brownian motion. The laser beam passes through the sample chamber and follows the path of scattered light through the particles in the suspension, so that the particles can be observed through a 20x magnification microscope with a camera. Einstein’s equation is used to calculate the hydrodynamic diameter of the particles.

In the manuscript titled “A Pilot Study of Urinary Exosomes in Alzheimer’s Disease”, enzyme-linked immunosorbent assay was used to detect the levels of Aβ1–42 and P-S396-
tau (normalized by CD63) in urinary exosomes derived from AD patients and matched healthy subjects. TEM and NTA were used to characterize the exosomes. Urinary exosomes from AD patients were found to contain higher levels of Aβ1–42 and P-S396-tau compared to those of matched healthy controls, and exosomes taken from AD patients were also more numerous. The difference in levels of Aβ1–42 and P-S396-tau and the disparate quantity of urinary exosomes between AD patients and healthy controls may provide a basis for early diagnosis of AD.

However, the sample size in this study is relatively small, and the sample may not be representative. Studies of pathological protein in urinary exosomes of patients with AD are relatively few, and the difficulty of operation and experimental uncertainty are higher than in detection of plasma exosomes. More samples are needed to verify the conclusion. In addition, the vesicles tested in the study included exosomes as well as other extracellular vesicles. If further purification is done using technology such as neuron-derived markers (NCAM or LiCAM antibodies), which only exist on the surface of neuron-derived exosomes, but not on other vesicles, the results will be more reliable [16].

Intracellular Aβ accumulation is the result of amyloid precursor protein (APP-transport imbalance where in extra proteins that exceed the degradation capacity of glial cells and lysosomes are released into the extracellular space among brain cells by exosomes [17-19]. Phosphorylated tau protein accumulation leads to the formation of double-stranded microfilaments that in turn accumulate to form neurofibrillary tangles and then destroy the normal function of neurons, eventually leading to the onset of AD [20]. In AD, the level of tau protein is 300% higher than in normal older adults, and hyperphosphorylated tau protein plays a major role in the progression of AD [21]. Upregulation and then failure of neuronal autophagic-lysosomal systems in patients with AD may cause lysosomal proteins to be added to exosome shipments, inappropriately facilitating their removal from neurons [22,23], so the level of lysosomal proteins in exosomes in patients with AD may be aberrant. The direct neuropathological consequences of insulin resistance include increased formation and accumulation of Aβ1-42 oligomer, increased level of tau phosphorylation, and higher levels of insulin in the brain, which can competitively inhibit the degradation of Aβ1-42 protease [24-26]. It can be concluded then that insulin resistance plays a key role in the disease process of AD. A decrease in the level of synaptic protein SNAP-25 is considered to be a biomarker indicating the degree of synaptic degeneration [27,28]. Loss of synaptic density and connectivity, accompanied by decreased expression of synaptic protein SNAP-25, has been observed in multiple brain regions of patients with AD.

Regarding treatment, only highly fat soluble substances with molecular weights below 400Da can reach the brain through blood circulation due to the blood-brain barrier. However, over 98% of drug molecules fail to meet this standard, so the effect of most drugs is limited [29]. In recent years, in order to improve intracranial drug delivery, researchers have used a variety of methods, such as surgery, infusion of hypertonic fluid, and drug chemical modification, to increase the permeability of the blood-brain barrier and consequently increase the total amount of drugs reaching the brain. However, this method also inevitably increases the risk of intracranial infection and may have more adverse effects on patients. Because its lipid bimolecular structure can effectively load hydrophobic and hydrophilic drugs, and can freely cross the blood-brain barrier [30], exosomes are also considered ideal carriers for drug delivery [31]. Exosomes’ lipid bimolecular structures can effectively load both hydrophobic and hydrophilic drugs [32]. In the process of ligand receptor-mediated drug delivery, exosomes facilitate targeting [33], laying a foundation for highly specific therapies for nervous system diseases such as AD.

AD is a progressive neurodegenerative disease. The vast majority of AD patients do not show any symptoms even in the few years immediately preceding the onset of dementia, although memory impairment may sometimes reach the threshold for diagnosis [34]. At this time, the effect of drug treatment is very limited, seriously affecting the quality of life of patients as well as their families. Therefore, the development of methods allowing early diagnosis before the clinical stage is imperative, because preventive treatment may be more effective. The study of exosomes has opened up a new path for the diagnosis and treatment of AD. It is believed that early diagnosis and treatment of AD will be finally possible with further study.

Conflicts of Interest

The authors have no relevant disclosures or conflicts of interest to declare.

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