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Review Article: Exosomes: Future Perspective in Neurodegenerative Diseases

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ABSTRACT

Neurodegeneration is a progressive and irreversible loss of neuronal cells in specific regions of the brain. Alzheimer Diseases (AD) Parkinson Disease (PD) are the most common forms of neurodegenerative diseases in older people. Exosomes are extracellular nanovesicles that have a key role in physiological processes such as intercellular communication, cell migration, angiogenesis, and anti-tumor immunity. Mounting evidence indicates the role of exosomes in neurodegenerative disorders as possible carriers of disease particles. They have several different potential applications thanks to their unique structure and functions. The present review summarizes recent studies on exosome potentials as a biomarker and therapeutic tool in neurodegenerative diseases. It also provides an overview of the structure and function of exosomes.

Keywords: Exosome, Neurodegenerative disease, MicroRNA, Biomarker

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Highlights

Exosomes as diagnostic biomolecules and therapeutic drug delivery system Exosomes in neurodegenerative diseases.

Introduction

Neurodegenerative diseases are characterized by loss of neurons in the central or peripheral nervous system which leads to losing their function and structure over time. Two common forms of neurodegenerative diseases are Alzheimer Disease (AD) and Parkinson Disease (PD). AD is the major cause of dementia in the world, accounting for 60%-70% of all demented cases [1]. It is related to permanent and progressive loss of memory and cognitive functions. The senile plaques containing amyloid β (Aβ) deposits and neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein are two pathological hallmarks of AD. Accordingly, there are two generally accepted hypotheses of the Aβ and the tau hypotheses. Based on the amyloid hypothesis, the imbalance between the generation and the clearance of Aβ is the main cause of AD [2, 3]. Aβ is formed by the continuous proteolytic cleavage of the amyloid precursor protein (APP) by β-secretase (beta-site amyloid precursor protein cleaving enzyme1, BACE1), and γ-secretase (consisting of presenilin1 and presenilin2).

Tau protein is a microtubule-stabilizing protein that modulates axonal transport. When tau hyperphosphorylates, it separates from microtubules and aggregates into insoluble fibers. NFTs are made of the hyperphosphorylated and dephosphorylated forms of tau. It is believed that tauopathies contribute to the severity of AD [4].

PD is the most common movement disorder. It affects almost 1% of the people over 50 years of age [5]. PD patients usually show disorders related to movement, including resting tremor, muscle rigidity, and cognitive malfunction as the disease advances. PD is characterized by Lewy bodies (LBs) in the substantia nigra pars compacta (SNpc) and striatum and progressive losing of dopaminergic neurons. LBs mostly comprise filamentous α-synuclein (α-syn). In PD patients, α-syn becomes abnormally phosphorylated and aggregated [6]. It has been suggested that LB impairs pathways, including vesicle trafficking or activating neuroinflammation [7].

Substantial evidence suggests that exosomes work as a vesicular conveyor for intercellular transmission in neurodegenerative disorders [8]. Recent studies indicate that exosome transport disease particles such as α-syn [9, 10], Aß, and prions from their original cells to other cells [11, 12]. Increasing documentation shows that microRNA (miRNA) is an important factor in AD and PD pathogenesis. In this regard, miRNA, a class of non-coding RNAs, have been considered as important regulators for post-transcriptional gene expression by either suppressing translation or degrading target mRNAs [13].

Since their findings, miRNAs have been recognized as the modulator mostly implicated in many vital biological processes, including development, growth, differentiation, and neurodegeneration [14]. One miRNA could choose many genes and a single gene could be regulated by several miRNAs. This feature makes miRNAs a potential tool to study multifactorial diseases like AD [15].

Regarding the important role of exosomes in neurodegenerative pathologies, this review spotlights the structure and function of exosomes, their role in AD and PD, and their potential as diagnostic or therapeutic agents.

Exosomes

Exosomes are small endosomal derived membrane vesicles of 30-150 nm in diameter with a cup-shaped morphology and a density of 1.13-1.19 g/cm2 that are released from different kinds of cells, including lymphocytes, dendritic cells (DCs), mast cells, platelets, endothelial cells, epithelial cells, and neurons. They can exist in many and perhaps all biological fluids such as blood, saliva, breast milk, amniotic fluid, plasma, urine, and so on [16-18]. These nano-sized biovesicles (exosomes) were first identified in 1983 by the John Stone Group [19].

Molecular content of exosomes

Exosomes have a complex and unique composition with various biomolecules (such as proteins, lipids, mRNAs, microRNAs [miRNAs], and DNA) [20, 21]. According to the latest ExoCarta database, almost a variety of 194 lipids, 4563 proteins, 1639 mRNAs, and 764 miRNAs have been determined in exosomes of several organisms [22]. The content of exosomes can be categorized into two groups: constitutive molecules and cargo molecules. Constitutive molecules play a crucial role in the structural and functional properties of exosomes and

based on the type of the derived cell, they are unique to the exosome. Cargo molecules include lipids, proteins, and various genetic materials that are resorted, encapsulated, and transported by exosomes. Cargo molecules are highly heterogeneous and vary based on the origin of the cell and the pathological or physiological conditions when exosomes create. Protein cargoes include heat shock proteins (Hsc70, Hsp90) and different types of tetraspanins (CD9, CD63, CD81, and CD82), flotillin, Rab GTPases, Alix, Tsg101; lipid cargoes have an essential role in regulating exosomal sorting of small RNAs and proteins. The genetic material cargoes consist of DNA and different types of RNA (mRNA, miRNA, rRNA, circular RNA, and long non-coding RNA [lnRNA]) [23].

The biological function of exosomes

Although exosomes were initially considered as cellular waste (garbage bags) or by-products of cell homeostasis, new data elucidate that exosomes are an alternative way to eliminate waste products from cell damage and maintain cellular homeostasis [24, 25]. The most attractive function of exosomes is as vehicles of lipids and proteins, which influence downstream signaling events in recipient cells and affect different features of physiology and cell behavior, such as nerve regeneration, synaptic function, and behavior [26].

It has been found that these extracellular vesicles have various functions in many cellular processes. They carry essential biological molecules from one cell to the other, regulate the microenvironment, and the genetic and epigenetic systems of cells [27]. They also participate in cell-cell communication, signal transduction, cell maintenance, and immune responses [28-32]. In addition, evidence shows that exosomes are also interestingly involved in angiogenesis, tumorigenesis, metastasis of tumor cells, and the transformation of normal cells into tumor cells. It has been reported that they respond to therapy through the transfer of oncogenes and oncomiRNAs between cancer cells [33, 34].

Evidence has revealed that exosomes have both positive and negative effects on the nervous system. According to studies, exosomes help develop the formation of the myelin sheath, growth of neurite, and survival of neurons. They are, therefore, important parameters in the regeneration and repair of tissues. Besides, exosomes in the CNS contain pathogenic proteins, such as Aβ peptide, and α-syn that may aid in disease progression. Therefore, exosomes in the brain through the transfer of misfolded proteins can also play a negative role in the creation of CNS diseases, such as stroke, AD, PD, and the like [35].

Exosome in Neurodegeneration

Alzheimer disease

Exosomes play a threatening role in the extension of toxic Aß pathology. Several studies have noted that exosomes serve as carriers for Aß transportation. A notable report by Rajendran et al. showed that the cleavage of APP by ß secretase happens in the particular endosomes and is transferred into multivesicular bodies (MVBs) from its original release location in company with exosomes. They reported that exosomal proteins such as Alix and flotillin-1 can accumulate around amyloid plaques in the brains of AD patients [36]. Further studies have shown that they may increase Aß production and deposition and inhibit Aß clearance [37].

In addition, exosomes increase abnormal tau phosphorylation. It has been reported that they carry phosphorylated tau protein and may be accountable for the extension of tau between cells in neurodegenerative AD conditions. Elevated levels of exosome-associated phosphorylated tau are easily detected in the cerebrospinal fluid (CSF) samples of early AD patients and reduce as the disease develops despite the increase in the total level of the protein, maybe because of separation of tau from the exosome fraction [38].

Parkinson disease

It has been shown that exosomes are involved in α-syn aggregation, transportation to the extracellular environment, and release of its toxic forms. Absorption of exosomes full of α-syn has been demonstrated to cause death in nearby neurons and leads to their dysfunction [6, 9].

Important evidence showed that mutations in some endocytic genes like leucine-rich receptor kinase 2 (LRRK2), and vacuolar sorting protein 35 (VPS35) are associated with PD. Based on studies, a mutation in LRRK2 causes an abnormal elevation in the quantity of morphologically distinguished MVBs. The creation of many MVBs could be the potential cause of the collection of exosomes loaded with the toxic form of α-syn and extension of the disease to adjacent neurons [39].

Exosome in neuroinflammation

Neuroinflammation is considered a chronic inflammation of the central nervous system. It is identified by

the activation of astrocytes and microglia. Activated microglial cells are required in an inflammatory response, stimulating the release of cytokines and chemokines, tumor necrosis factor-α (TNF-α), TNF-β, nuclear factor-κB, and enzymes like 5-lipooxygenase (5-LOX), 12-LOX, and cyclooxygenase 2 (COX-2) [38].

Exosomes have the key role as cargo of inflammatory molecules. Therefore, they are considered inflammatory mediators. It has been reported that they may promote neuroinflammation due to communication between neurons and glia [38, 40].

Besides, neuroinflammation can trigger Aβ pathogenesis and tau hyperphosphorylation which are two important hallmarks of AD. Gupta and Pallim have shown that Aβ is packaged into exosomes and extends between cells, beginning an inflammatory cascade [38]. In the early stage, the stimulation of microglia by Aβ has a neuroprotective effect because it can phagocyte and degrade Aβ. The microglia activation by astrocyte secreted ATP cause to release of exosomes as a protective strategy to prevent astrocyte signaling [41]. In the later stage, microglia release exosomes comprising pro-IL1 b, active caspase-1, and soluble toxic Aβ. All of them damage nerve cells [42].

Also, it has been shown that astrocytes can internalize α-syn deposits. This phenomenon is related to the later formation of inclusion bodies, as found in PD patients' brains and the beginning of an inflammatory response. moreover, exosomes released by activated microglia are the important moderator of neurodegeneration, which is induced by α-syn [43].

Exosomes as diagnostic and therapeutic biomarkers

In recent years, various studies have revealed that exosomes and their cargo molecules are indicative of pathophysiological conditions and a better reflection of the cellular processes. Recent studies show that they can be used as valuable prognostic and diagnostic biomarkers of various diseases [16], such as chronic inflammation [44], cardiovascular and renal diseases [45, 46], lipid metabolic diseases [47], cancer progression [48], and neurodegenerative diseases [49].

To date, there is still no cure for neurodegenerative diseases such as AD and PD that can alter or stop its development, although, there are various medications for AD and PD that can improve symptoms in some patients. It should be noted that many of these drugs have side effects.

Discovering new biomarkers can provide an early diagnosis of AD, which is very important and valuable for stopping and delaying the progression of the disease [37]. Exosomes can be detected in CSF and peripheral body fluids and can cross the blood-brain barrier (BBB) and are greatly stable in the peripheral circulation. Studies have shown that the content of exosomes will change with the occurrence of disease. Therefore, using exosomes as an appealing target for biomarker development in CNS diseases is an interesting prospect due to its potential to track disease progression and enable early diagnosis and treatment optimization [35].

Recent studies propose that the existence of Aβ1-42 or tau in the CSF exosomes can be a useful diagnostic indicator for the early diagnosis of AD. In these patients, plasma and CSF exosomes contain full-length tau contrary to the healthy people [50]. Also, the existence of Aβ1-42 in CSF exosomes could be a sensitive scale for recognizing AD. The detection of both tau and Aβ 1–42 in CSF can help diagnose AD 10 years before the clinical symptoms [51]. Interestingly, new studies show that the level of each exosomal biomarker and the respective CSF biomarker are strongly correlated [52].

In Alzheimer disease, miRNA changes may be found both in the brain, CSF, and other biological fluids. It has been reported that miRNA sequences can be deregulated in the peripheral blood of AD patients. Several studies have determined differences in miRNA concentrations between normal people and Alzheimer disease blood, making its potential as a diagnostic procedure. It is worth noting that miRNAs exhibit higher sensitivity levels compared to protein biomarkers, which is mainly a consequence of the amplification of polymerase chain reaction (PCR) [53-56]. The role of exosome in clearance is vital in AD [57]. Because of this important ability to elevate Aβ clearance, it has been suggested that exosomes have potential in the treatment of AD [58].

In Parkinson disease, recent research has been reported multiple roles for exosomes, including neurotoxic and neuroprotective roles, diagnostic biomarkers, and the application as a drug delivery system [59, 60].

Gui et al. and Cao et al. in separate studies appraised the existence of miRNAs in exosomes from the CSF and serum of PD patients [61, 62]. A different profile of significantly upregulated and downregulated miRNAs in exosomes of PD patients in comparison to healthy people was analyzed. These miRNAs can regulate genes that are involved in different pathways for PD.

Result of recent studies show that some miRNAs, including miRNA-155, miRNA-7, miRNA-124, miRNA-205, miRNA-34b/c, and miRNA-7116-5p have therapeutic potentials and miRNA-1, miRNA-19b-3p, miRNA-153, miRNA-409-3p, miRNA-10a-5p, miRNA-19b, miRNA-195, and miRNA-24 are important biomarkers in different diseases. These findings strongly support the idea that miRNA exosomes are potentially a valuable diagnostic and therapeutic tool in PD.

Result of recent studies on miRNA-155, miRNA-7, miRNA-124, miRNA-205, miRNA-34b/c, and miRNA-7116-5p as therapeutic potential, and miRNAs, miRNA-1, miRNA-19b-3p, miRNA-153, miRNA-409-3p, miRNA-10a-5p, miRNA-19b, miRNA-195, and miRNA-24 as biomarker miRNAs strongly indicate the diagnostic and therapeutic value of miRNA exosomes in PD [61-64]. Lemprière mentioned exosomal α-syn as a biomarker for PD [65].

It is suggested that exosomes (synthesized or obtained from the natural cell) can be applied as nano-particle tools for the delivery of therapeutic drugs, proteins, miRNA, and siRNAs. Exosomes can pass the BBB and enter the targeted cells to release their cargoes for therapeutic roles [66, 67]. Qu et al. reported that loaded exosomes with dopamine had a better therapeutic effect with less toxicity than free dopamine by a structured intravenous administration in the PD mice model [68]. These findings, therefore, show that the PD animal models benefit from the transfer of genetic materials such as miRNAs within mesenchyme stem cells (MSCs)-derived exosomes. This method is therefore considered an effective tool, provides a potential treatment for PD. Therefore, understanding how these miRNAs exosomes communicate with the cells and molecules in PD is substantial. Although increasing evidence for the role of exosomes in the pathogenesis of PD and AD has been found, the mechanisms within the molecules that control and modulate exosome secretion, biogenesis, and communication with recipient cells should be still defined [69].

Conclusion

The discovery of exosomes as diagnostic biomolecules and therapeutic drug delivery systems in many diseases such as neurodegenerative diseases are highly promising. Above all, isolating safer exosomes for diagnosis, therapy, and prognosis requires more standardized purification technologies that should be progressed.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki, 2013.

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Authors' contributions

Both authors equally contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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