Extracellular Vesicles from Mammalian Cells in Neurodegenerative Diseases

Subjects: Neurosciences

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A growing number of studies have indicated that extracellular vesicles (EVs), such as exosomes, are involved in the development of neurodegenerative diseases. Components of EVs with biological effects like proteins, nucleic acids, or other molecules can be delivered to recipient cells to mediate physio-/pathological processes. For instance, some aggregate-prone proteins, such as β-amyloid and α-synuclein, had been found to propagate through exosomes. Therefore, either an increase of detrimental molecules or a decrease of beneficial molecules enwrapped in EVs may fully or partly indicate disease progression.

Keywords: extracellular vesicles ; outer membrane vesicles (OMVs) ; plant-derived exosome-like nanoparticles (PDELNs) ; neurodegenerative diseases

1. Behaviors and Functions of Mammalian EVs

The uptake of EVs is mediated in several ways, including endocytosis, phagocytosis, and direct fusion with the plasma membrane. It has been demonstrated that the anchor proteins of the surface membrane of EVs can interact with membrane receptors on recipient cells, and this “ligand–receptor” interaction mediates the uptake of EVs by their target cells [1]. To address this mechanism, investigators used specific inhibitors or antibodies to block receptor–ligand interactions, revealing that the uptake of EVs was significantly hampered in a variety of cell types, which demonstrated that receptor-mediated endocytosis contributes to the uptake process of EVs [2][3][4][5][6]. Additionally, another study showed that some EV membranes were able to fuse directly with the plasma membrane of the recipient cells by labelling melanoma cell-derived exosomes with the lipid fluorescent probe Octadecyl Rhodamine B Chloride (R18) [7]. These studies together suggested that there are several known mechanisms underlying EV uptake, and the cells of different types or with different functions may choose a different manner of EV uptake to complete EV-mediated intercellular communication. Below is a table that lists several types of EV uptake.

2. Role of EVs of Mammalian Cells in Neurodegenerative Diseases

EVs play a double role in the central nervous system. On the one hand, disease-associated proteins can be propagated by EVs shuttled between different cells. As the disease develops, these proteins spread from one focal point in the brain to a larger scope of neuronal regions, accelerating the progression of neurodegeneration [8][9]. EVs containing disease-associated proteins involved in Prion disease, Parkinson’s disease (PD), Alzheimer’s disease (AD), and amyotrophic lateral sclerosis (ALS) have all been found in the cerebral spinal fluid (CSF) and blood of patients affected by these disorders [10]. Prion diseases are a group of rare progressive neurodegenerative diseases, including Creutzfeldt–Jakob disease (CJD), Gerstmann–Straussler–Scheinker disease, and kuru [11][12]. It is now widely accepted that the misfolding of the host-encoded prion protein, PrP^{C}, into a disease-associated transmissible form, PrP^{SC}, results in the transmission of pathology not only between cells but also from one region to another [13][14]. Both forms of prion proteins were found to be shuttled by exosomes [15]. Exosomal PrP^{SC} was found to transmit protein aggregation in rabbit kidney epithelial cells [16]. Subsequent in vivo experiments showed that exosomes derived from prion-infected mice were able to transmit aggregation to naïve mice [17][18]. For many years, PrP^{SC} involved in prion disease was the only known transmissible protein for the spread of disease, but recent studies using both animal and cellular models have confirmed that other proteins related to neurodegeneration are also transmissible. This includes α-synuclein in PD, and tau and Aβ in AD [19]. For example, EVs are an efficient carrier of α-synuclein aggregation and propagation between neurons, thus promoting the progression of PD [20]. Furthermore, EVs circulating in the blood and CSF of patients with PD have been found to be highly enriched with α-synuclein and are remarkably correlated with the stage of the disease [21]. For AD, it has been shown that neurotoxic, oligomeric forms of Aβ protein are wrapped in EVs isolated from brain tissue, and these vesicles can mediate the inter-neuronal propagation of Aβ [20]. To testify the critical role of EVs in AD development, an in vivo study

revealed that injecting 5xFAD mice (AD model mice) with neutral sphingomyelinase 2 (nSMase2), an inhibitor of exosome secretion, significantly reduced amyloid plaque formation in the brain [17]. In addition, another study demonstrated that, as carriers of Aβ, astrocytes-derived extracellular vesicles (ADEVs) are involved in the pathogenesis of AD [22]. In the brain, astrocytes phagocytose too much fibril Aβ42 to digest them, which causes a severe accumulation of intracellular Aβ. To avoid further intracellular stress, astrocytes release undigested fibrils of Aβ42 via EVs, which would, in turn, lead to severe neurotoxicity in neighboring neurons [23]. Also, in ALS patients, astrocytes can generate EVs, which are toxic and lead to adjacent motor neuron death [24]. Furthermore, ADEVs mediate the propagation of neuroinflammation as well as regulate mutual signaling between the brain and the immune system. In a mouse model of inflammatory brain injury, ADEVs rapidly enter the peripheral circulation, inducing an acute peripheral cytokine response to accelerate the migration of peripheral leukocytes to the brain, thereby triggering neuroinflammation [25]. The above experimental data suggested that ADEVs in the peripheral blood might serve as a source of biomarkers for neurological disorders.

On the other hand, EVs act as a scavenger that can remove aggregation-prone misfolded proteins of cellular/intercellular space, exerting a neuroprotective effect [26]. As shown by investigators, the correctly folded prion protein (PrP^C) on EVs could trap neurotoxic β-amyloid (Aβ) to promote its fibrillation. In this case, the role of PrP^C-contained exosomes is to remove Aβ to diminish its neurotoxicity and prevent the accumulation of misfolded proteins [17]. Additionally, in order to take advantage of the neuroprotective role of mammalian cell-derived EVs, numerous studies have concentrated on the therapeutic effect of stem cell-derived EVs, especially on mesenchymal stromal cell-derived EVs (MSC-EVs) [27][28][29][30][31][32]. It was initially found that mesenchymal stromal cells (MSCs), isolated from bone marrow or adipose tissues, can significantly mitigate neurodegeneration [31][33]; later, investigators confirmed that even MSC-EVs themselves can strongly alleviate cognitive impairment caused by brain injury, stroke, or neurodegeneration [34][35][36], accompanied by obvious neuron regeneration throughout the ventricular region, cingulated gyrus, and hippocampus [37][38][39]. MSCs have the strong ability to migrate and differentiate, interacting with brain parenchyma to release vascular endothelial growth factors (VEGFs), nerve growth factors (NGFs), brain-derived neurotrophic factor (BDNFs), and other bioactive molecules to promote the regeneration of blood vessels and nerves, and the reconstruction of neural synapses, as well as to prevent neuron apoptosis [40][41][42][43]. In addition, MSCs can restrict the release of inflammatory molecules like prostaglandins and interleukins to minimize neuroinflammation [44][45]. The above beneficial effects that MSCs display depend on their paracrine function rather than on direct interaction with the diseased site [29][35]. It was later verified that the conditioned medium of cultured MSCs showed a similar therapeutic effect to that of MSCs themselves [46][47]. More interestingly, EVs isolated from an MSCs-cultured medium showed almost the same protective effect as MSCs [45][48].

The exact mechanism underlying the neuroprotective role of MSC-EVs remains ambiguous. Generally, MSC-EVs have bioactive contents that include cytokines, growth factors, signaling lipids, and regulatory microRNAs, which can influence tissue rehabilitation after injury, infection, or disease [45]. For example, over 900 varieties of protein molecules in MSC-EVs have been identified using proteomics technology, including neprilysin, a protease that can degrade Aβ oligomer [49]. In addition, Egor A. and colleagues found that MSC-EVs exert a neuroprotective role via preventing calcium overload in an PI3K/AKT-dependent manner [34].

3. The Potential of MSC-EVs as a Biogenic Drug for Treating AD

In the pathogenesis of AD, a high level of homocysteine in plasma (hyperhomocysteinemia, HHcy) is an independent risk factor [50][51][52][53]; HHcy AD mice show an increased Aβ level in the brain [54]. In homocysteine metabolism, insufficiency of 5-methlytetrahydrofolate (the active form of folate) would result in an accumulation of its upstream substrate, homocysteine [55], which is consistent with another study showing that a folate-deficient diet can also accelerate brain amyloidosis in an AD mouse model [56]. Meanwhile, investigators have indicated that high folate intake decreases the risk of AD [57]. However, sufficient dietary intake of folate does not mean that it is efficiently delivered to the brain; in particular, the blood–brain barrier (BBB) excludes most of the free folate in the plasma. The efficient delivery of folate to the brain parenchyma largely depends on the specific recognition of folate-receptor α (FRα), which is shuttled by EVs derived from choroid plexus epithelial cells [58][59][60]. Therefore, only with the help of FRα shuttled by exosomes can folate can be smoothly transported through the BBB to reach the neurons or glia.

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