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Recent progress in neurodegenerative diseases via exosomal therapy

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Abstract

Exosomes are the type of extracellular vesicles (EV) found almost in every type of biological fluid from human blood to saliva and semen. These EVs are rich in various kinds of nucleic acids such as DNA, RNA and proteins. They mediate in cell-to-cell communication and transfer cargo to different cells and tissues. In the brain, they perform a variety of functions i.e., synaptic plasticity, neuronal stress response and neurogenesis. Though much research has been carried on exosomes revealing their character in tumor proliferation and neurodegenerative diseases, their exact role and function in mental disorders remains scarce. Exosomes are permeable to blood-brain barrier due to this permeability they be hypothesized as potential biomarkers of neural dysfunction. Study on exosomes precisely those derived from the brain may deliver information about theranostic and may offer a mechanistic approach of the phenotype of the disorder. In this review paper, we highlight the role of exosomes in neural degenerative diseases.

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Introduction

Exosomes (Exos) are extracellular carriers (EV) originate from late endosomes that are produced by intraluminal budding of endosomal membranes in multivesicular bodies. These EVs are released into the extracellular space when multivesicular bodies fuse with the plasma membrane [1]. There are two destinations for multivesicular bodies, either it can be fused into the lysosome, leading to the self-destruction, or merged with the plasma membrane, releasing its intraluminal vesicular ILV components in the form of Exos.

Exosomal Physiology and functions

Exos are composed of a lipid bilayer, molecular components of their cellular origin, proteins and RNA (**Figure 1**). Exos reflect the composition of the cells from which they originate; therefore, they are also called the mini version of the primary cell [3-5]. However, an exosomal protein may differ in the cell and its original tissue, and the Exos may consist of an evolutionary protein molecule. The content of Exos may reflect its regulated storage mechanism. Exos are composed of several proteins including enzymes, transcription factors, lipids, receptors, EV matrix enzymes, nucleic acids such as DNA and RNA inside and on the surface of Exos. Analysis of the protein composition of Exos showed that some proteins arise specifically from cells and tissues of origin, and some are common among all Exos. [6-8] Exos play a significant role in the cell-to-cell communication, and these interactions over the past decade have been of great interest. Previously, they were clinically diagnosed as cancer vaccines, capable of promoting tumor-derived exposomes to angiogenesis and metastasis [9, 10] and injecting BM-derived progenitor cells [11]. Exosome communication mainly transports protein and RNA into neighboring cells or to distant organs (**Figure 1**). [12,13] Earlier, Exos derived from curcumin-derived tumors accumulate in microglial cells and relieve brain inflammation. Once outside the cell, the most important task of emergence is to communicate from cell to cell. Exos conveys their signal through systemic circulation to their maternity cells or other cells, including neighboring cells and remote one. [14-16] There are a plethora of exosome-related pathological and physiological functions in the central nervous system (CNS). As Exos have been shown to play a role in neuronal development and activity, Exos are involved in neurodegenerative disorders such as the pharynx, Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease [17-22]. It is well-known that Exos can transport proteins from one cell to another, thereby helping the spread of disease in the brain [8]. Concerning clinical relevance, it is important to understand the external pathological and physiological roles of the brain [23,24]. This goal cannot currently be achieved due to the inability to isolate the original Exos from the brain for additional research.

In addition to the traditional extraction of Exos from biological fluids, for instant urine, cell culture medium, blood, or CSF, many technical issues must be resolved to maximize the isolation of vesicles with similar physiological and/or molecular properties. To minimize the isolation of membranes hidden as Exos, cell integrity should be maintained to a great extent, careful precision of vesicles is required to confirm the enrichment of Exos compared to mimetics, and biophysical and biochemical interpretation of Exos is required. Recently, efforts have been put to characterize Exos l release and absorption for their role in the CNS. Earlier work has shown that Exos and their cargo play role in normal communication of the central nervous system, along with synaptic function, plasticity, nerve regeneration, and the immune response [25-26]. Along with their crucial role in regular brain function, Exos are also involved in the spread of neurodegenerative disorders [27,28]. In the anomaly, physiological conditions of the brain and other CNSs such as Parkinson's disease and Alzheimer's disease Exos are primary educators for the rest of the body [29-30]. Given their contribution to diseases, it is reasonable to believe that Exos are responsible for the pathogenesis of brain diseases

Exosomal role in neuro-pathobiology

Exos are detected to be responsible for the strategies that were previously linked to the psychopathology of mental disorders, such as neuroinflammation [31], neurogenesis [32], plasticity, and epigenetic regulation [33]. Furthermore, exosomes ability to surpass BBB proposes that exosome contents in the CSF may mirror undergoing neural developments [34]. Consequently, exosomes derived from neurons may act as potential biomarkers of mental diseases. As mentioned before, these extracellular vesicles can work as an important source of communication. Several researchers have shown that exosomal

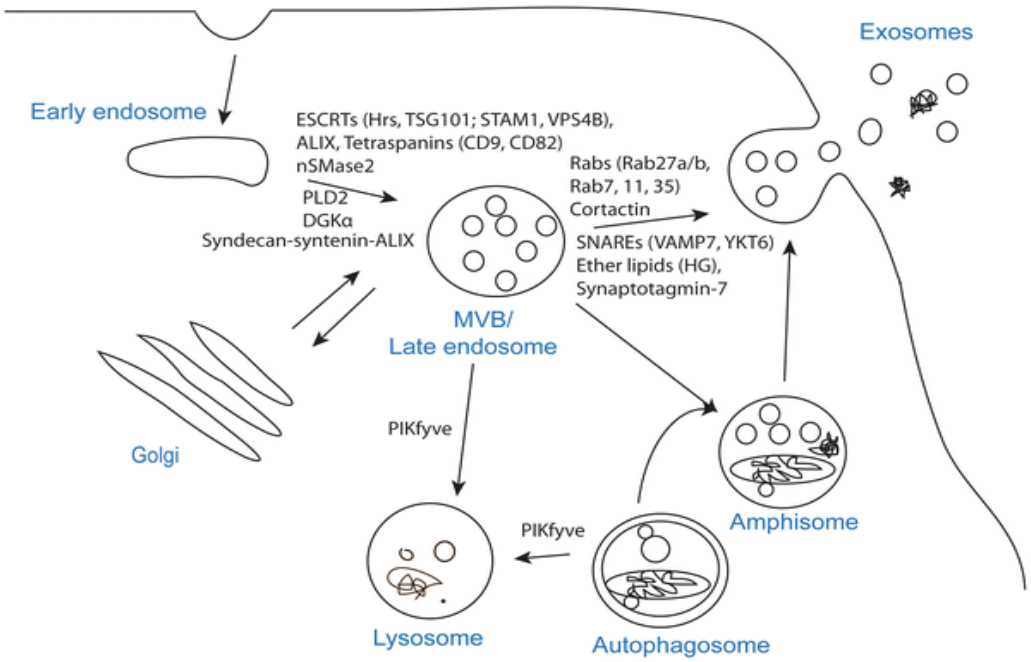

Fig. 1: The brief description of formation of exosomes inside parental cell and molecules affecting their biogenesis and release. The figure has been adapted from Ref. [68], copyrights 2019 Springer Nature Limited.

release from CNS is regulated by the synaptic glutamatergic and calcium entry [35-36]. Besides, the controlled release of neural exosome has been acknowledged; however, the complete mechanism is still uncertain [37]. In axon, MVBs are in an abundant amount as compared with soma or dendrite [38]. Though the procedure of favoured compartmentalization is not known, these specific zones of enhancement also confirm the role of synaptic Exos and their highly regulated release.

Serotonin also facilitates the release of Exos from the non-neuronal cell in the brain. [41]. Dysregulation of serotonin pathways has been hypothesized to be responsible for anxiety, bipolar disorder, and schizophrenia. Because serotonin can regulate the microglial release of Exos and serotonin is often compromised in mental disorders, the release of microglial Exos may also be altered in these disorders. The release of neurotransmitters and cellular communication are important factors in psychopathology [42]. It is therefore imperative understanding the role that Exos play in the etiopathogenetic of mental disorders, as they are important for the regulation of cellular communication and its regulation via neurotransmitters.

Communication between neurons can occur through the release and uptake of Exos by phagocytosis or pinocytosis. Notably, it has been shown that a subpopulation of neuron-internalized Exos can be secreted with the endogenous Exos of the recipient neuron, apparently facilitating extensive interactions, as shown in **Figure 2** [42,43,52]. Although the destiny of Exos not certain yet, these results prove that the ability of Exos to facilitate in the communication within the cell and its potential for signal transference [43]. Also, signalling from neurons to neurons via Exos is involved in important processes, including synaptic plasticity (**Figure 2**). Similar to a feedback loop, the release of neurotransmitters may stimulate secretion of oligodendrocyte Exos, while neurons can internalize oligodendrocyte Exos and use their charge.

The internalization of exos derivatives of oligodendrocyte can cause bearing huge pressure and better cell viability, causing cell protection weight in the brain; their ability to cross the BBB. Latest findings on the characteristics of Exos signal in the brain relate to the existing physio-pathological perceptions of mental disorders (**Figure 2**). Since the first discovery that the transport of exosomal cargo in the recipient cell has functional effects, several studies of this mechanism have been performed via cell-to-cell communication in disease states and health conditions. For instance, the ability of exosome replicating and inducing an effect on receptor cells has been recognized as a potential pathway linked to the progression of neoplastic cells. Exos extracted from colon neoplastic cells express a mutated form of the K-RAS protein.

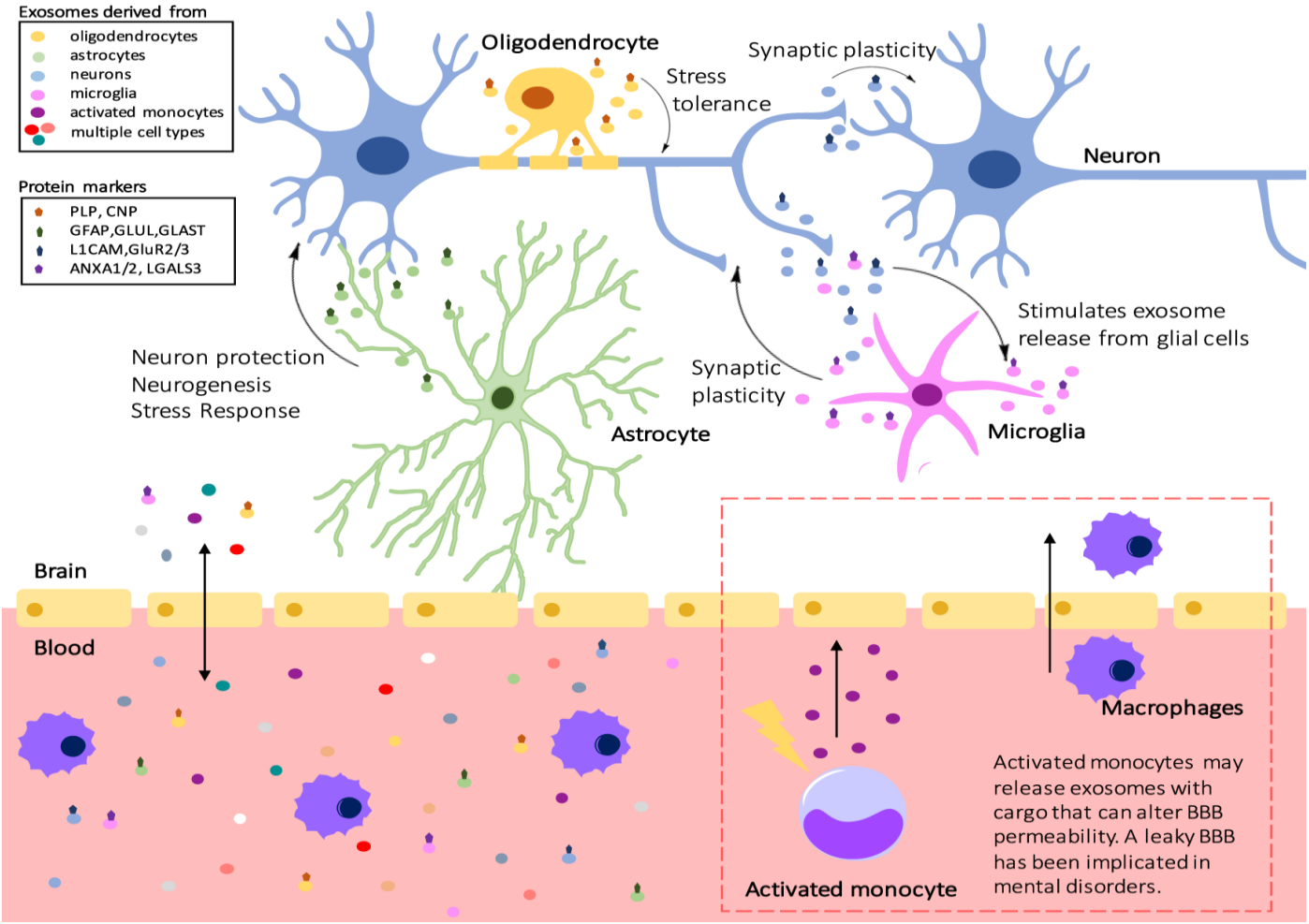

Fig. 2: The Function of neural Exosomes. Exos signalling is mediated in numerous physiological brain functions. Changes in exosomes derived from the brain have been already related to mental disorders. Such as actuated monocytes discharge exosomes which may impact BBB permeability. The figure has been adapted from Ref. [51], copyrights 2019 Springer Nature Limited.

K-RAS comprises of mutant KRAS and many enzymes that can endorse cancer progression. These Exos, which can be internalized by wild-type colon cells, can transfer the mutant protein to healthy cells, leading to increased growth of these cells [44].

Exosomes as a potential Biomarkers

In the brain, it has been shown that communication via Exos plays a role in the progression of Alzheimer's disease through the transport of misfolded beta-amyloid oligomers from neuron to neuron [45]. Using an in vitro model, formation and secretion of Exos were blocked by siRNA inactivation of the proteins required for these functions, and oligomer multiplication was also blocked [45]. Though some phenotypic and mechanistic dissimilarities between cancer and mental disorders, we believe in quantitative and non-dichotomous changes of both anomalies. Nevertheless, the consequences of this study prove that Exos can spread diseases via cargo transfer. Meanwhile, miRNAs have been implicated in mental disorders, Exos miRNA transfer may contribute to both phenotype progression and distinct symptoms. It would be interesting to investigate miRNAs related to psychiatric phenotypes and whether or not these Exos miRNA profiles are changed in brain disorders [46-47]. The ability of Exos to surpass BBB is of significant importance as it makes them as particularly decent biomarkers for neural degenerative disorders.

Presently, most research is related to the specific cells' exosomes from cell culture media, though, Exos from other cells are of diverse importance, and there has been the latest surge in the significance of recognizing Exos of a particular source from organic liquid [48]. Various types of Exos (From multiple

types of cell) can be extracted from biofluids using a couple of methods i.e., ultracentrifugation, immunomagnetic beads, and chromatography. Furthermore, Exos consist of lipid bilayer; consequently, RNAse treatment before use will guarantee that cargo has been loaded within vesicles [49]. This mixed population of Exos may be recognized through different techniques such as western blots or mass spectrometry. However, many known biomarkers are not suitable for Exos identification, hence additional characterizations of Exos is needed. Since exosomes are mini versions of their parental cell, it is realistic to enrich Exos extracted from a certain cell of mixed population using specific cell biomarkers.

Exos discharged from hippocampal neurons comprises of L1 cell adhesion molecule and the GluR2/3 subunits of glutamate receptors. These both are widely accepted biomarkers. Protein markers, such as glutamine synthetase, glutamine aspartate transporter and glial fibrillary acidic protein may be used to develop exosomes from astrocyte. Moreover, myelin proteolipid and 2', 3'-cyclic nucleotide 3'-phosphodiesterase have been recognized for Exos derivatives of oligodendrocytes. In the field of diseases diagnosis, this can be of greater importance due to its connections to the marker and mechanisms of disease. Recently various studies have been carried on neuron-derived Exos to answer questions related to neurodegenerative diseases from blood plasma biopsies. Sun et al. used Exos extracted from plasma to augment neuron derived Exos. They revealed that the number of exosomes derived from neurons together with levels of Amyloid β -proteins, High-mobility group box 1, and neurofilament light, can play the role as biomarkers of neuropsychological injury in HIV82. Exomes derived from neurons plasma has also been used to carry trials to examine protein biomarkers for patients suffering from MDD87. [51-53].

Exos Based strategies in Brain Diseases

Similar to other exos neural exos are also comprised of complex cargo such as proteins and nucleic acids and also, they are play key role in numerous biological functions, such as immune regulation, communication, bioenergetics, tissue regeneration, and metabolism. Due to their inter-cellular trafficking, they can affect endocrine or pancreatic cellular process. Because of their diagnostic applications, existence in various body fluids, and is less invasive exos derived from MSC are symbolized as ideal theranostics candidate [54].

Researcher are considering exsosomal therapy as a leading candidate to effectively treat neurological diseases, as they are responsible in the activation of regenerative process in diseased. Mesenchymal stomal exos offer beneficial therapeutic, additionally their small size allows them to be managed easily. Ryosokue et. al designed exos to treat Parkinson disease. They developed EXOsomal Transfer into Cell, which was able to deliver therapeutic designer exos rescued neuroinflammation induced by systemic injection of LPS (**Figure 3**).

Additionally, according to some researchs, exos derived from human adipose MSC are comprise of functional neprilysin, (a major Aβ-denigrating protein) and, therefore, have the likely to lessen the neurotic accumulation of Aβ in AD, the expression of miR-21 in MSC-derived exos play role in improvement and modulation of cognitive function in APP/PS1 double transgenic model of AD [55-57]. Cui et. al have used miRNA-181c expression in MSC-exos that caused reduction in inflammation caused by burn, miRNA-181c expression down regulating the receptor 4 signalling pathway. They also targeted brain by exos derived from MSCs, by means of usage of peptide RVG, in order to upsurge the effectiveness of intravenously conveyed exos. Then by tail vein the RVG engineered exos were supervised by intravenous admission to APP/PS1 transgenic mice to detect its therapeutic effect by Morris water maze test. Plaque accretion was detected by Thioflavin-S staining and Aβ collection were detected by ELISA [58].

Engineered exos, accompanied by RVG merged with Lamp2b, may powerfully carry miR-124 to the infarct site after ischemia. The cyclo (Arg-Gly-Asp-D-Tyr-Lys) peptide [c (RGDyK)] displays great similarity to integrin αvβ3, where its expression on endothelial cells is provoked via ischemia [59,60]. Targeted delivery of c (RGDyK)- conjugated exos has caused in a robust clampdown of the inflammatory response in the lesion section behind cerebral ischemia [61]. The GE11 peptide has high similarity to the epidermal growth factor receptor and GE11-positive exos that is comprised of the miRNA let-7 and exos were capable to avoid cancer [62]. Furthermore, other proteins that can dock exos are connexin 26 [64] tenascin C and connexin 43 [63].

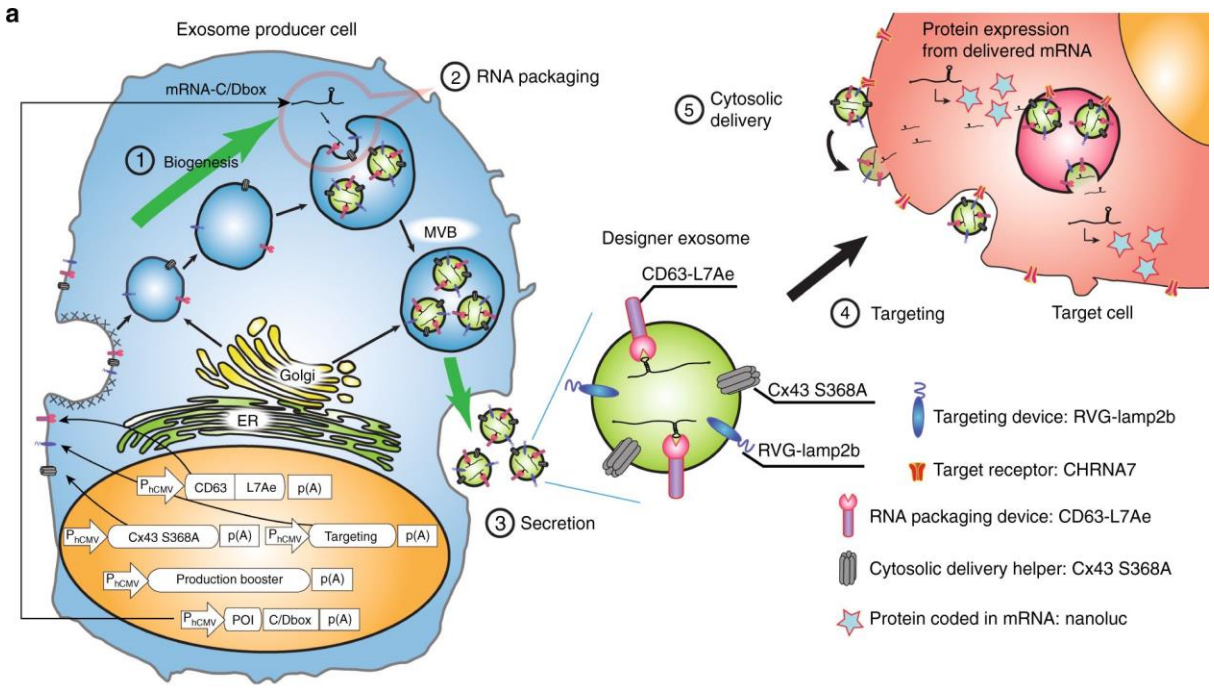

Fig. 3: Diagram of the EXOtic devices. Exos comprising of RVG-Lamp2b to target CHRNA7, CD63-L7Ae, Cx43 S368A and mRNA were powerfully manufactured by exo manufacturer cells via exosome construction booster. The modified exos were conveyed to target cells and the mRNA was carried to the target cell cytosol via cytosolic delivery helper. Lastly, protein programmed in the mRNA was articulated in the target cells. The figure has been adapted from Ref. [55], copyrights 2019 Springer Nature Limited.

Future Perspectives

Despite the study on exosomes is comparatively new, there are some strong proofs from other fields suggesting that the study of Exos may provide insights into mechanisms and processes related to mental disorders. Presently, research on exosomes is related to exosome's role in cell-to-cell communication. Nevertheless, additional work needs to be done on the mechanism of bidirectional transfer of Exos through the BBB. Exosomal psychiatry should be on main focus for future perspectives. Exosomes isolated from CNS has a huge potential of biomarking as they may reveal physiological changes in mental diseases that may be reached at the periphery.

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