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Review

Exosomes: A missing link between chronic systemic inflammation and Alzheimer's disease?

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ABSTRACT

Exosomes are potent mediators of physiological and pathological processes. In Alzheimer's disease and inflammatory disorders, due to exosomes' distinctive ability to cross the blood-brain barrier, a bidirectional communication between the periphery and the central nervous system exists. Since exosomes can carry various biochemical molecules, this review investigates the role of exosomes as possible mediators between chronic systemic inflammatory diseases and Alzheimer's disease. Exosomes carry pro-inflammatory molecules generated in the periphery, travel to the central nervous system, and target glial and neuronal cells. Microglia and astrocytes then become activated, initiating chronic neuroinflammation. As the aging brain is more susceptible to such changes, this state of neuroinflammation can stimulate neuropathologies, impair amyloid-beta clearance capabilities, and generate dysregulated microRNAs that alter the expression of genes critical in Alzheimer's disease pathology. These processes, individually and collectively, become significant risk factors for the development of Alzheimer's disease.

Search strategy and selection criteria

References for this Review were identified by searches on PubMed and ScienceDirect between the dates 1985 and September 2022 and references from relevant articles. The search terms "exosomes," "Alzheimer's disease," "chronic systemic inflammation," "chronic systemic inflammatory diseases," "pro-inflammatory cytokines," "extracellular vesicles," "neuroinflammation," "systemic inflammation and infection," "rheumatoid arthritis and neuroinflammation," "systemic lupus erythematosus and neuroinflammation," "blood-brain barrier," "microgliosis," "microglial priming," and "astrogliosis" were used. There were no language restrictions. The final reference list was generated based on relevance to the topics covered in this review; only two chronic systemic inflammatory diseases were included (Rheumatoid Arthritis and Systemic Lupus Erythematosus), while other chronic systemic inflammatory and autoimmune diseases were excluded to get a general and concise view on the matter. Extracellular vesicles other than exosomes were also excluded, as the study's purpose is to investigate the role of exosomes in this bidirectional communication between the systems. Finally, neurodegenerative diseases other than Alzheimer's disease were excluded since the central focus of this Review is Alzheimer's disease and the role of exosomes in mediating this disease.

Abbreviations: EVs, extracellular vesicles; MVs, microvesicles; CME, clathrin-mediated endocytosis; CIE, clathrin-independent endocytosis; ESE, early sorting endosome; EE, early endosome; MVEs, multivesicular endosomes; MVBs, multivesicular bodies; ER, endoplasmic reticulum; ILVs, intraluminal vesicles; ESCRT, endosomal-sorting complex required for transport; AD, Alzheimer's disease; NDD, neurodegenerative disease; NFTs, neurofibrillary tangles; Aβ, amyloid beta-peptides; APP, amyloid precursor protein; PHF, paired helical filaments; *PSEN,, presenilin*; *APOE,, apolipoprotein E*; SCI, chronic systemic inflammation; DAMPs, damage-associated molecular patterns; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; CNS), central nervous system; WM), white matter; CRP, C-reactive protein; BBB, blood-brain barrier; LPS, lipopolysaccharide; APP-Tg mice, APP transgenic mice; WT, wild-type; IL, interleukins; RAGE, receptor for advanced glycated end products; ABC transporter, ATP-binding cassette transporter; P-gp, P-glycoprotein; TNF-α, tumor necrosis factor-alpha; PolyI:C, polyriboinosinic-polyribocytidylic; β-secretase, beta-secretase; BACE1, β-site APP cleaving enzymeI; α-secretase, alpha-secretase; CTFs, C-terminal fragments; **γ**-secretase, gamma-secretase; AICD, APP intracellular domains'; MCI, mild cognitive impairment; IFNγ, interferon-gamma; miRNA, microRNAs; siRNA, short-interfering RNA; ncRNA, non-coding RNAs; lincRNAs, long intergenic noncoding RNAs; TLRs, toll-like receptors; MSCs, mesenchymal stem cells.

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1. Introduction

1.1. Exosomes

Extracellular vesicles (EVs) are membranous nanoparticles produced and released by all types of cells and found in the extracellular matrix [1,2]. EVs were first identified as cellular waste products in the 1980s [3,4]. Advances in research now classify EVs as crucial players in intercellular communication and signaling [5]. EVs are evident in a wide diversity of biological fluids, including urine, blood, cerebrospinal fluid, saliva, breast milk, plasma, and serum [1,5–7]. Based on EVs' origin, function, and biogenesis, they can be categorized into three types: apoptotic bodies, microvesicles (MVs), and exosomes (Fig. 1A) [7,8]. Exosomes are the smallest EVs, range from 30 to 150 nm in diameter, and are generated and secreted through the endosomal pathway [8]. A single cell can release different EVs, and heterogeneity exists even in each EV type [10]. Furthermore, current experimental tools for isolating and characterizing exosomes and other EVs still need technological improvement; due to these methodological limitations, it is not easy to distinguish exosomes entirely from MVs. However, to maintain the integrity of this review article with the relevant literature, ’exosome’ as a term would be used throughout the text.

Exosomes are generated through the endosomal pathway (Fig. 1B); extracellular molecules are internalized into the cell through clathrin-mediated endocytosis (CME) or clathrin-independent endocytosis (CIE), forming an early sorting endosome (ESE), also known as early endosome (EE). The ESE grows and develops into multivesicular bodies (MVBs) [8], also known as multivesicular endosomes (MVEs) [5,6]. The MVB resides near the endoplasmic reticulum (ER) and the trans-Golgi network, which aids in the uptake and modification of the intracellular cargo [1]. The cytosolic molecules, including proteins, lipids, DNA, and RNA, will be taken up by the MVB by the invagination of the membrane, forming other membranous vesicles inside the MVB known as intraluminal vesicles (ILVs) [1,2,8]. ILVs can sort the cargo through two different pathways; (a) the endosomal-sorting complex required for transport (ESCRT) complex-dependent pathway and (b) the ESCRT complex-independent pathway. The ESCRT-dependent complex contains protein complexes ESCRT-0, ESCRT-I, ESCRT-II, ESCRT-III, and their accessory proteins [8]. The first three ESCRT protein complexes (ESCRT-0, -I, -II) have ubiquitin-binding domains to interact with the ubiquitinated cargos found in the proximity of the MVB and recruit them onto the membrane of the MVB [2,8]. ESCRT-III and its accessory proteins promote the inward budding of the MVB’s membrane, invaginating the cargo into the MVB in the form of ILVs. As for the ESCRT-independent complex, the pathway requires tetraspanins and lipids in membrane rafts for the trafficking of the cargo [8]. Once the MVB contains numerous ILVs, it can have one of three fates; (1) fusion with lysosomes, where the contents become degraded, (2) fusion with apoptotic bodies if the cell is undergoing apoptosis, and (3) fusion with the plasma membrane, in which the ILVs and the cargo are released into the extracellular space in the form of exosomes [2,8]. After the release of exosomes into the extracellular matrix, they could either transport their cargo to a cell at a proximal distance or travel long distances to influence different recipient cells [9,11]. Depending on their exosomal surface

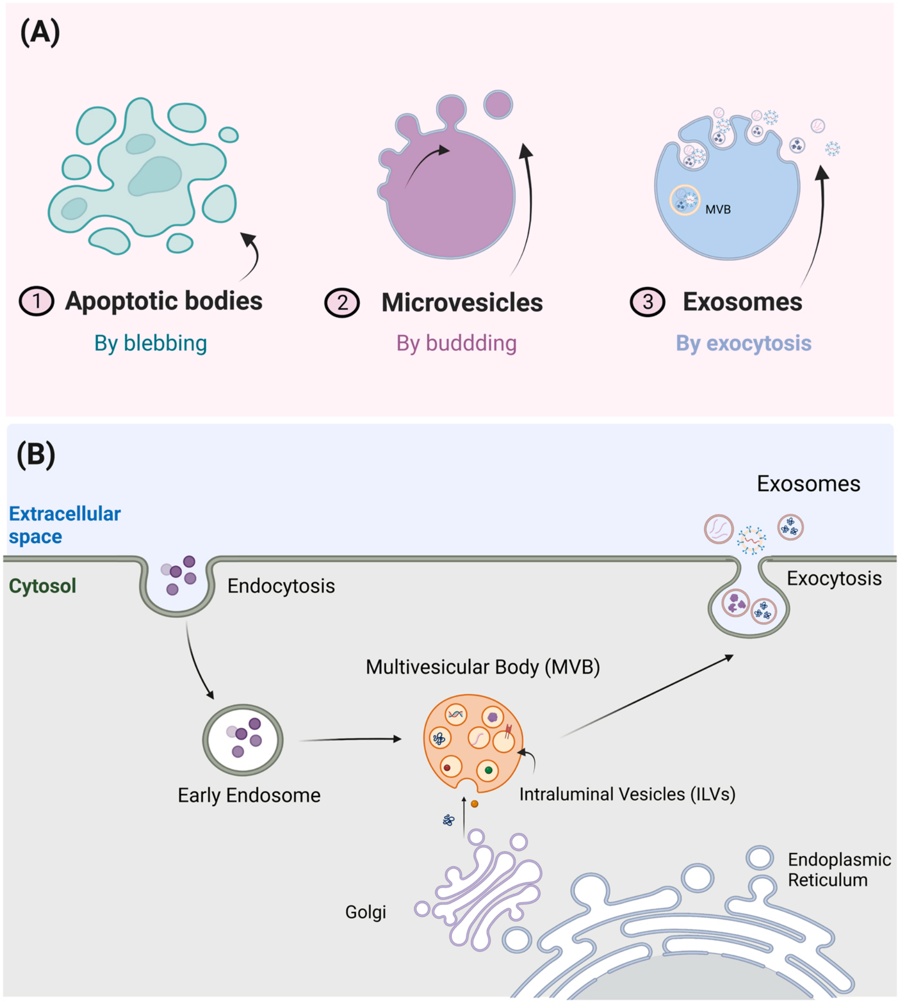

Fig. 1. The Three Types of Extracellular Vesicles and Exosome Biogenesis. (A) There are three types of extracellular vesicles (EVs) that are distinguished based on biogenesis and size [7,8]; (1) Apoptotic bodies are the largest (1000–5000 nm in diameter), and they are formed by "blebbing" off from the cellular membrane of a cell going through apoptosis. (2) Microvesicles (MVs) (100–1000 nm in diameter) are formed by budding outwards of the plasma membrane, and (3) exosomes (30–150 nm in diameter), which originate from the endosomal system [7]. (B) Through the invagination of the plasma membrane (endocytosis) of cargo from the extracellular space, an early endosome is formed [5,6,9]. The early endosome grows near the endoplasmic reticulum (ER) and the trans-Golgi network as these organelles assist in the uptake and modification of the intracellular cargo. The early endosome becomes a multivesicular body (MVB)/ multivesicular endosome (MVE) [1]. The cytosolic molecules, including proteins and RNA, will be taken up by the MVB through the invagination of the MVB’s membrane, forming other membranous vesicles inside the MVB known as intraluminal vesicles (ILVs) [1,2,5,6,8]. The MVB fuses with the plasma membrane and releases the ILVs in the form of exosomes into the extracellular matrix through exocytosis [1,2,5,9]. Created with BioRender.com.

proteins and the cellular receptors on target cells, they can become internalized by the recipient cells through various mechanisms [7,12]. After internalization, due to the intercellular transfer of the exosomal contents, many cellular processes can be influenced [6].

1.2. Alzheimer's disease: a neurodegenerative disease

Alzheimer's disease (AD) is the most common neurodegenerative disease (NDD) and dementia, especially in people above 65. AD is a progressive disease that causes impairments in behavioral and cognitive functions [13]. The speed of the progression of the disease and the reduction in cognitive abilities are based on individual variations [14]. This discrepancy can be due to external environmental factors and internal conditions affecting the disease's initiation and progression [15]. Patients with AD present pathological changes in the brain; at a macroscopic level, the changes include brain shrinkage along with atrophy, cortical thinning due to synaptic deficits, and progressive neuronal cell death. These manifestations are due to microscopic changes, which include mitochondrial damage, impairment of axonal transport, oxidative stress, depositions of abnormal extracellular neuritic plaques, intraneuronal neurofibrillary tangles (NFTs), and consequences of neuroinflammation [13,15]. The neuritic plaques, also called senile plaques, are spherical microscopic lesions with amyloid-beta peptides (Aβ) formed by the proteolytic cleavage of the amyloid precursor protein (APP). APP can be cleaved by beta-secretase (β-secretase), also known as β-site APP cleaving enzyme I (BACE-1), or by alpha-secretase (α-secretase) to produce C-terminal fragments (CTFs), which will be further cleaved by gamma-secretase (**γ**-secretase) generating APP intracellular domains (AICD) and various peptides (A$\beta_{1\text{–}40}$, A$\beta_{1\text{–}42}$, and others) (Fig. 2A) [13,16]. Amyloid deposition can stimulate the activation of microglia and astrocytes, damage axons and dendrites, and result in loss of synapses [15]. The NFTs are intracytoplasmic structures formed primarily by the hyperphosphorylation of the microtubule-associated protein tau. Due to the extracellular Aβ plaques, tau becomes abnormally phosphorylated, triggering its aggregation. Aggregated tau and phosphorylated tau then combine to form twisted pairs of helical filaments (PHF), which further come together to create the NFTs [6], resulting in neuronal loss [16]. AD's genetic causes include mutations in *APP*, *presenilin 1 (PSEN1)*, and *presenilin 2 (PSEN2)*, and the presence of the ε4 allele of the *apolipoprotein E* (*APOE*) gene

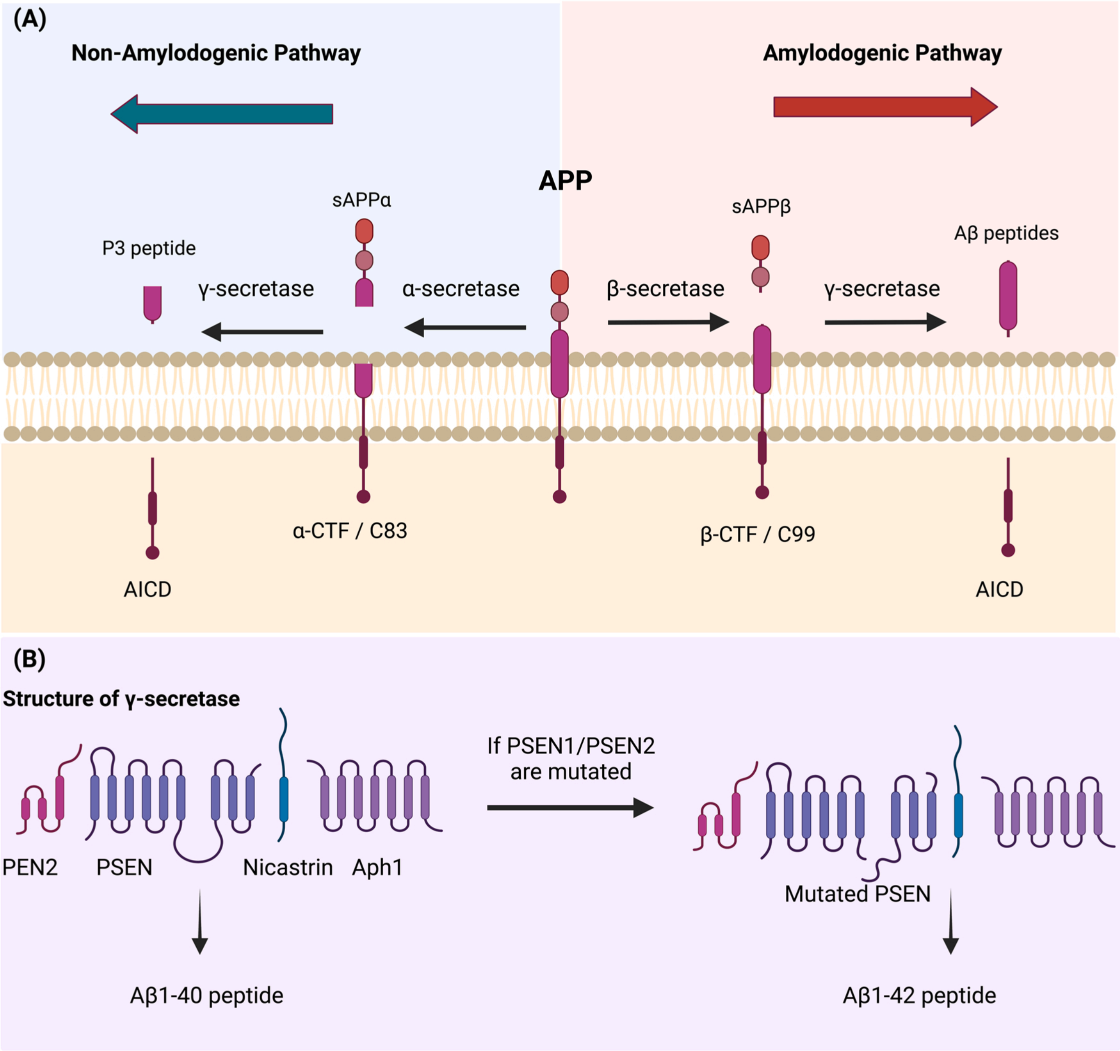

Fig. 2. The Processing of APP Through the Amyloidogenic and Non-amyloidogenic Pathways. (A) Amyloid precursor protein (APP) is cleaved by β-secretase or α-secretase, which produces C-terminal fragments; β-CTF (C99) or α-CTF (C83). The CTFs are cleaved by γ-secretase to produce 'APP intracellular domains' (AICD) and peptides. In the case of C83, its cleavage will yield AICDs and P3 peptide, while in the case of C99, its cleavage will yield AICDs and varying lengths of amyloid-beta (Aβ) peptides (A$\beta_{1\text{–}40}$ and A$\beta_{1\text{–}42}$). The latter pathway is known as an amyloidogenic pathway since A$\beta_{1\text{–}42}$ has amyloidogenic properties, making it susceptible to aggregation and depositions in plaques [16]. (B) Mutations in *Presenilin 1* and *2 (PSEN1, PSEN2)* lead to a partial loss of function in γ-secretase; APP is incompletely digested, resulting in the production of amyloidogenic amyloid-beta (A$\beta_{1\text{–}42}$) [15,18]. Created with BioRender.com.

[17]. *APP* gene, located on chromosome 21, is a type I transmembrane protein whose cleavage produces Aβ peptides and other protein fragments. *PSEN1* and *PSEN2* are homologous genes found on chromosomes 1 and 14, respectively. PSEN1/2 are proteins that play a role in activating the γ-secretase complex [15]. There are 150 mutations in *PSEN1* and 10 in *PSEN2* that lead to a partial loss of function in γ-secretase. Consequently, APP can be incompletely digested, resulting in fewer Aβ peptides generation; however, more Aβ_{1-42} is formed than Aβ_{1-40}, which contributes to AD development since Aβ_{1-42} is more amyloidogenic (Fig. 2B) [15,18].

1.3. *Chronic systemic inflammation*

Chronic systemic inflammation (SCI), in most cases, is triggered by the release of damage-associated molecular patterns (DAMPs) without the presence of infectious agents, making it a persistent, maladaptive, non-resolving, and low-grade type of inflammation [19,20]. SCI diseases have a heterogenous pathogenesis; there is no one main predominant risk factor and mechanism for their appearance [20]. One of the most prevalent risks of developing SCI is an increase in age [19]. Studies have revealed that older individuals have elevated levels of pro-inflammatory cytokines and chemokines circulating and elevated expressions of genes correlated with chronic inflammation, which is known as "inflammaging" [21]. Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) were chosen as examples of SCI disorders in this review article for several reasons. (1) RA and SLE are highly prevalent SCI and autoimmune diseases with evident dysregulation of both the innate and adaptive immune responses [22,23]. (2) The clinical onset of both of the diseases is multifactorial, with the interaction of environmental, hormonal, and immunological factors and the presence of genetic predispositions [23,24]. (3) RA and SLE are heterogenous in the age of onset and severity and progression of the manifestations. The age of onset of SLE ranges between 15 and 44 [24], and between 50 and 80 in RA [25]. The onset age of RA is a clear indication of the relationship between the pathology of this disease with the “inflammaging” phenomena. As for SLE, the onset age is much earlier compared to RA, however, due to the chronic nature of SLE, the CNS is under pathological inflammatory insults for longer periods, and this is essential to be investigated regarding AD initiation. Moreover, it is well known that in AD specifically there is a presymptomatic phase characterized by the accumulation of Aβ without any evident clinical symptoms [14] and this prodromal phase which lasts for years can overlap with the age range of RA. From this perspective, the widespread inflammatory conditions of both RA and SLE might be crucial to consider in the development of AD. In addition, the symptoms, severity, and extent of manifestations in RA [25] and SLE [24] can differ significantly from patient to patient. Patients can present different grades of systemic inflammation throughout the development and progression of the diseases making RA and SLE potent SCI diseases to investigate concerning the initiation of neuroinflammation and NDDs. (4) Even though both SLE and RA are a result of autoimmune causes, their immunological responses and mechanisms of initiation are different; in RA, there is an initial activation of the innate immune system, with the activation of macrophages and fibroblast-like synoviocytes (FLS) being the major contributor to the inflammatory process, whereas in SLE, all innate immune cells can induce the inflammation with the complement system dysfunction being the major contributor. Regarding the innate immune response in RA, there is an initial increase in the number of FLS, which results in the production of metalloproteinases that break down the extracellular matrix. The high levels of FLS also increase the expression of chemokine receptors, which further contributes to the proliferation of the FLS. This stimulates the generation of pro-inflammatory cytokines that lead to the infiltration of natural killer cells, macrophages, neutrophils, and dendritic cells to the joints. The pro-inflammatory cytokines along with exogenous molecules, pathogen-associated molecular patterns (PAMPs), and endogenous molecules, DAMPs, initiate the chronic inflammation cascade seen in RA [23]. In SLE, the innate immune response is triggered by abnormalities in complement proteins. A deficiency in C1q results in an impaired phagocytic ability of the macrophages to clear apoptotic bodies and immune complexes. As a result, the immune complexes accumulate in organs and trigger tissue damage, and produce more apoptotic bodies. The apoptotic cells can lead to an increase in the self-antigens levels, which bind to dendritic cells. This results in antigen presentation to autoreactive B-lymphocytes leading to the generation of autoantibodies and activation of the autoimmune response. Neutrophils also result in the loss of peripheral self-tolerance by activating Toll-like receptors and overproducing reactive oxygen species. Natural killer cells also generate high levels of interleukin (IL-4) and interferon-γ (IFN-γ) resulting in cytotoxicity [23]. (5) Last but not least, SLE and RA are also correlated with higher chances for the patient to develop dementia and cognitive dysfunction [5,26,27], indicating, along with the other reasons given above, the importance of their investigation in AD susceptibility.

Symptoms of SCI diseases can range from mild to severe and include fatigue, decreased appetite, anhedonia, increased sleep, depression-like symptoms, and social withdrawal, collectively known as "sickness behaviors." Severe consequences of SCI include increasing the individual’s susceptibility to and promoting the initiation of type II diabetes, cardiovascular disease, autoimmune diseases, depression, cancer, NDDs, etc. [19]. Thus, it can be said that SCI may be implicated in both initiating and exacerbating NDDs. This review will explore the role of SCI in the development of AD and the mechanism through which this communication occurs.

2. SCI disorders & Alzheimer’s disease

To begin, patients who develop delirium due to an SCI disease display the evident link between systemic inflammation and the central nervous system (CNS) [28]. Research has shown that the possible transfer of inflammatory molecules and signals to the CNS alters the cytokine milieu in the CNS, resulting in many consequences, which are all elaborated further in detail below.

2.1. *White matter structural abnormalities*

A study has shown that a moderate systemic inflammation induced in newborn mice results in alterations in the development of white matter (WM) and MRI abnormalities, followed by myelination deficits and cognitive impairments [29]. In addition, Walker et al. [30] examined the role of systemic inflammation on the WM structure in patients. The systemic inflammation was characterized by the levels of C-reactive protein (CRP) detected and their results demonstrated that individuals suffering from systemic inflammation after midlife show higher WM structural abnormalities in their later lives. They also showed that when systemic inflammation started at early ages (ages 40–50) and persisted until 70, it had an even higher correlation with WM structural abnormalities. However, individuals with high levels of CRP in midlife and then lower levels later in life had a lower risk of acquiring WM structural abnormalities. Their results suggest that the persistence of systemic inflammation (such as in SCI diseases) is the main contributor to structural and neurodegenerative changes in individuals with a higher risk of dementia and neurological dysfunction [30].

2.2. *Alteration of the Blood-Brain Barrier’s Integrity*

Systemic inflammation can modify the permeability/ integrity of the blood-brain barrier (BBB). Takeda et al. [31] administered lipopolysaccharide (LPS) in the periphery to Alzheimer APP transgenic mice (APP-Tg mice) and wild-type (WT) mice [31]. LPS is naturally found in the cell wall of gram-negative bacteria and can activate the glia in the CNS [32]. After administration, brain inflammatory cytokines, including some interleukins, such as IL-6, were seen at much higher levels in the

APP-Tg mice than in the WT mice [31]. The APP-Tg mice also showed severe sickness behaviors after LPS administration and a more permeable BBB [31]. A more permeable BBB could enhance the peripheral immune cell infiltration into the CNS [33–35], increasing the brain's susceptibility to neuroinflammation in WT animals and contributing to the severity of the cognitive and behavioral symptoms in animal models with AD [31]. In another in-vivo study, which had a mouse model of SLE and mice injected with LPS, demonstrated that due to systemic inflammation, microglial cells travel to the BBB, and express tight-junction proteins, such as Claudin-5, to maintain the BBB's integrity and contact endothelial cells. However, as the inflammation is sustained/-chronic, the microglial cells become reactive and start to phagocytose essential BBB constituents and astrocytic end-feet leading to leakage across the barrier and infiltration of systemic molecules. The inhibition of some of these reactive microglia at the late stages of the inflammation showed a reduction in the permeability of the BBB, further confirming their findings [36]. Another study portrayed that the complement system activation, in response to SLE, can disrupt the BBB's integrity in rodents and an in-vitro two-dimensional BBB model with endothelial cells and astrocytes. Their findings showed that (1) the exposure of the BBB to the serum of SLE resulted in actin cytoskeleton rearrangement, and (2) the exposure to the complement component, C5a, resulted in tight junction proteins alterations, both consequences resulting in a disrupted BBB integrity [37]. Moreover, Aβ can generally transport across the BBB from the periphery to the CNS and vice versa through specific receptor-mediated pathways. The receptor for advanced glycated end products (RAGE) and its ATP-binding cassette transporter (ABC transporter), P-glycoprotein (P-gp), regulate the influx of Aβ to the brain [38]. A study showed that a rat model of RA had a higher expression of both P-gp and RAGE. Also, after administering Aβ intravenously, significantly higher amounts of Aβ were found in the hippocampus compared to the controls, confirming that higher quantities of Aβ were transported into the brain and specifically into the hippocampus. Thus they claim that RA can contribute to the initiation of AD by directly affecting the influx of Aβ from the periphery to the hippocampus, decreasing the BBB's integrity and the clearance capability of Aβ, and triggering neuroinflammation [38]. In addition, a study exhibited that administering a tumor necrosis factor-alpha (TNF-α) blocker to patients with RA resulted in lower peripheral blood levels of proteins related to BBB dysfunction compared with patients without the TNF blocker treatment [39].

2.3. *Microglial priming & microgliosis*

One of the potent mechanisms through which an SCI can exacerbate NDDs is microglial priming [40]. Microglial cells are heterogeneous; once they detect disrupting changes in the homeostatic balance of their local environment, they change their phenotype and morphology from M2 to M1 depending on the severity of the stimulus [41,42], similar to the macrophages in the periphery. One of the events altering the homeostatic balance is SCI diseases; the prolonged exposure of pro-inflammatory cytokines and factors from systemic inflammation primes the microglia (Fig. 3) [28,43]. This M1 phenotype promotes a neuroinflammatory cascade, has abnormal phagocytosis, and higher expression of pro-inflammatory cytokines, chemokines, reactive nitrogen species, and reactive oxygen species [17,44,45].

In a study, mice exposed to an inflammation prenatally, through the exposure of viral polyriboinosinic-polyribocytidylic (PolyI:C), showed that this exposure is ample enough to prime the microglia and trigger AD-like pathologies in their adulthood [46]. PolyI:C induced a prenatal immune challenge by triggering the expression of pro-inflammatory cytokines in the fetus's brain. Interleukins (such as IL-1α, IL-1β, and IL-6) were found in high levels and remained high even while aging. Consequently, altered phenotypes of microglial cells were seen in the CA1 stratum of the hippocampus with significantly elevated levels of APP, CTFs, AICD, and Aβ peptides, and across all hippocampal subfields an increase in phosphorylated tau was evident, resulting in cognitive impairment [46]. Similarly, LPS administration peripherally in mice also results in microglia activation and high TNF-α and IL-1β levels in the CNS [47]. Another study showed that RA could induce microglia activation in the hippocampus of mice. As a result, high levels of pro-inflammatory cytokines (such as IL-1β) were secreted in the hippocampus and triggered neuroinflammation in the brain [48]. Concerning AD, research demonstrates that the release of TNF-α, IL-6, and IL-1β from microglia can upregulate kinases that hyper-phosphorylate tau in neuronal cells, spreading tau to other neurons in the

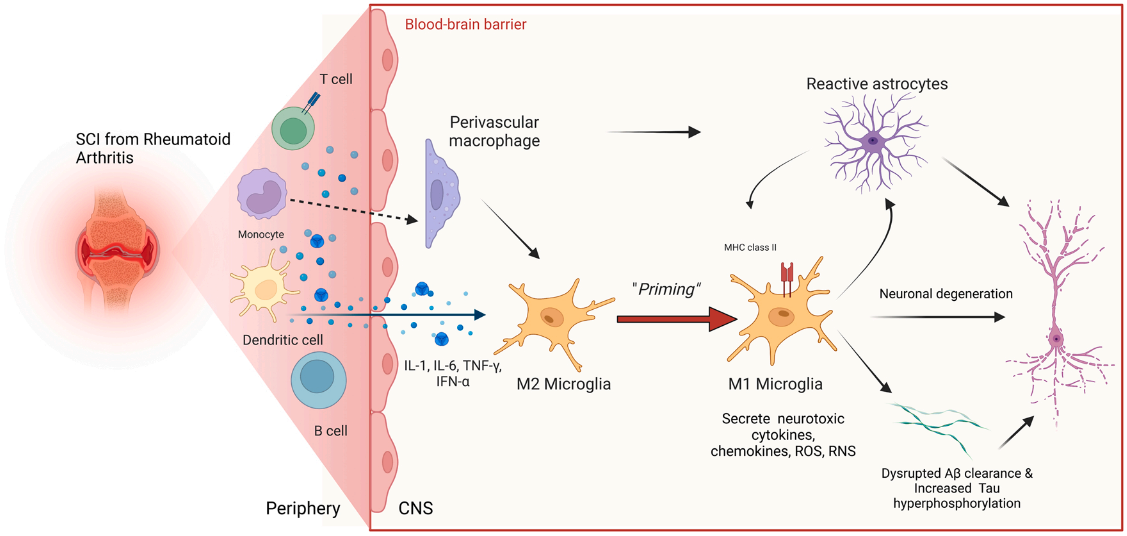

Fig. 3. Microgliosis and Astrogliosis in Response to a Systemic Chronic Inflammatory Disease. Systemic chronic inflammatory (SCI) diseases, such as Rheumatoid Arthritis (RA), result in the release of pro-inflammatory cytokines and factors from peripheral immune cells. The prolonged exposure of these factors to the central nervous system activates astrocytes and primes the microglia from the M2 phenotype to M1 [28,40–43,59]. The M1 phenotype results in an exaggerated release of pro-inflammatory cytokines, chemokines, reactive nitrogen species (RNS), and reactive oxygen species (ROS) [17,44,45]. Reactive astrocytes will also secrete pro-inflammatory factors, and further activate the microglia [54–56], demonstrating a feed-forward inflammatory loop. Consequently, the neuroinflammatory cascade begins along with a disrupted amyloid-beta (Aβ) clearance capability of the microglia and an increase in hyperphosphorylation of tau. These ultimately result in neuronal degeneration [49–51]. Created with BioRender.com.

hippocampus and initiating cognitive dysfunction and neurodegeneration [49–51]. In other studies, elevated levels of CRP in patients' blood are correlated with two times increased probability of developing mild cognitive impairment (MCI) and can be seen even five years before the diagnosis of MCI [51,52]. To address this link, postmortem brain tissue samples of RA patients showed that high CRP levels could trigger microgliosis and result in cognitive impairment. By administering a human TNF-α antibody peripherally in mice, inflamed microglia returned to their original phenotype, demonstrating that the microglia's phenotype could be restored to normal by inhibiting/reducing the pro-inflammatory cytokines in the periphery, such as TNF-α [53].

2.4. Astrocyte activation & astrogliosis

Once microglial cells are primed and activated upon an SCI, the pro-inflammatory cytokines released can also activate astrocytes, making them reactive and harmful. Astrocytes will also secrete pro-inflammatory factors, which further activate the microglia and the infiltrated peripheral immune cells; hence there is a feed-forward inflammatory loop between the cells of the CNS, leading to a state of chronic neuroinflammation and the initiation of neurodegeneration [54–56]. Astrocytes can also become reactive in response to a systemic inflammation, the breakdown of the BBB, and the release of pro-inflammatory factors from endothelial cells [55,57–59]. A study [55] demonstrated that culturing astrocytes with TNF-α, IL-1α, and C1q transformed the astrocytes into their inflammatory/ reactive state [55]. Another study done on rodents, presented that the breakdown of the BBB led to the buildup of blood-borne factors, including fibrinogen and immunoglobulins in astrocytes, which resulted in evident neuronal dysfunction seen in the rodents [60]. An experiment conducted on APP/PS1 mice also showed that when astrocytes are severely reactive, they trigger irreversible cognitive deficits and neurodegeneration [61]; this is most evidently detected in the entorhinal cortex and its axonal projection areas, which are critical in the development of AD. Thus, research shows that astrogliosis upon an immune challenge results in neuronal death, amyloid-like plaques, and metabolism dysregulation [46].

2.5. Neuroinflammation

As evident, the persistent glial activation in the CNS can lead to chronic neuroinflammation. This resultant neuroinflammation can accelerate both the expression and processing of APP and increase the extracellular accumulation of Aβ. In a study, LPS administration to the APP-Tg mice resulted in an accelerated Aβ deposition. Although normal Aβ accumulation is seen at 20 months of age in these mice, after the administration of LPS, the Aβ deposits were initiated at 12 months of age, and the APP levels were doubled with evident high numbers of severe astrocytic and microglial activation and proliferation in the neocortex and hippocampus [62]. In another study, mice (2 months of age), without APP/PS1 transgenes having osteoarthritis induction, exhibited neuroinflammation and Aβ plaque formation at age 4 months but the neuroinflammation was resolved after 6 months of age. Mice models without APP/PS1 genes and osteoarthritis induction lacked the Aβ plaque pathology, and mice with the APP/PS1 transgenes and osteoarthritis induction showed an accelerated and exacerbated AD pathology that continued throughout the mice's lifetime. Thus a transient induction of Osteoarthritis was enough to trigger AD pathology, but persistent exposure to the inflammation (such as in SCI diseases) is needed to continue the progression of neuroinflammation and AD pathology [63].

Furthermore, research demonstrated that the brain regions most vulnerable to peripherally-induced neuroinflammation include the cortex, amygdala, hypothalamus, and hippocampus. Thus, infiltrating pro-inflammatory and neurotoxic molecules can result in AD pathologies [64]. A case-control study of 56 million patients deduced that TNF produced systemically by macrophages, in response to RA and other SCI diseases, can cross the BBB through receptor-mediated transcytosis and significantly increase the risk of the patient for developing AD. The study also revealed that patients on TNF blockers correlated with a reduced risk for AD. As TNF blockers cannot readily cross the BBB, they sequester the TNF systemically, inhibiting them from invading the brain, consequently preventing neuroinflammation and delaying/averting AD development [65]. Other SCI diseases, such as SLE, also result in the activation of the complement system66, which is correlated with the instigation of neuroinflammation and tau pathology [67,68]. Studies have demonstrated that the downregulation of specific complement proteins such as C3, C3ar1, and C1q halted the progression of tau pathology, neuroinflammation, and synaptic loss [67,68]. Thus, these studies provide a consensus view that persistent systemic inflammations can trigger neuroinflammation by (1) disrupting the blood-brain barrier's integrity, (2) infiltrating pro-inflammatory factors and complement components, and (3) activating reactive glial cells, all resulting in a more vulnerable CNS to the initiation of AD.

2.6. Gene modifications

Other studies have explored the role of pro-inflammatory cytokines (TNF-α, IL-1β, and interferon-gamma (IFNγ)) on Aβ formation through the upregulation of genes related to β and γ-secretase activities [69,70]. For example, Lee et al. [71] demonstrated that repeated systemic inflammation (by LPS administration) could promote amyloidogenesis in WT mice by activating some APP-related secretases (β- and γ-secretases) and inhibiting others (α-secretase). Hence $A\beta_{1-42}$ accumulation was seen in the hippocampus and cerebral cortex of the mice, along with neuronal death, and memory impairments [71].

3. Role of exosomes in SCI & AD

There are various pathways by which inflammatory mediators influence the CNS and promote neuroinflammation and molecular changes [72]. Fig. 4 presents a proposed model for the communication pathways between the periphery and the CNS, which could be observed in AD. Multiple lines of evidence have demonstrated that exosomes can influence immunological diseases and NDDs by being carriers of DAMPs, chemokines, tissue-degrading enzymes, misfolded proteins, autoantigens, microRNAs (miRNAs), and cytokines [73–76]. These exosomes are used in intercellular communication by spreading and propagating their cargo [6]. Depending on the biological state of the original cell whether it is activated, resting, or diseased, it modulates the packaging of the inflammatory cargo and its secretion [73].

3.1. Exosomes as cytokine carriers

All cytokines can be packaged into and transported by EVs; this was proven valid for 33 cytokines. They can be either encapsulated or attached to the surface of the exosomes; if the exosome contains surface cytokines, then they will target cells containing the corresponding specific cytokine receptors [75]. A study demonstrated that dendritic cells activated by LPS showed an elevated amount of exosomes carrying inflammatory cytokines. These exosomes were taken up by epithelial cells, which led to their activation and the further release of pro-inflammatory molecules [77]. Moreover, the advantages of encapsulating cytokines were explored; firstly, the cells could use this process to eliminate over-produced cytokines. Secondly, exosomes can protect cytokines from degradation by shielding them from trypsin digestion. Thirdly, cytokine delivery is expedited since they can travel longer distances and affect distant recipient cells, thereby increasing the possibility of cytokines to influence cells that are usually not targeted when cytokines are released in the cell's immediate environment. Thus even if the number of cytokines carried by the exosomes is little, their impact is significant

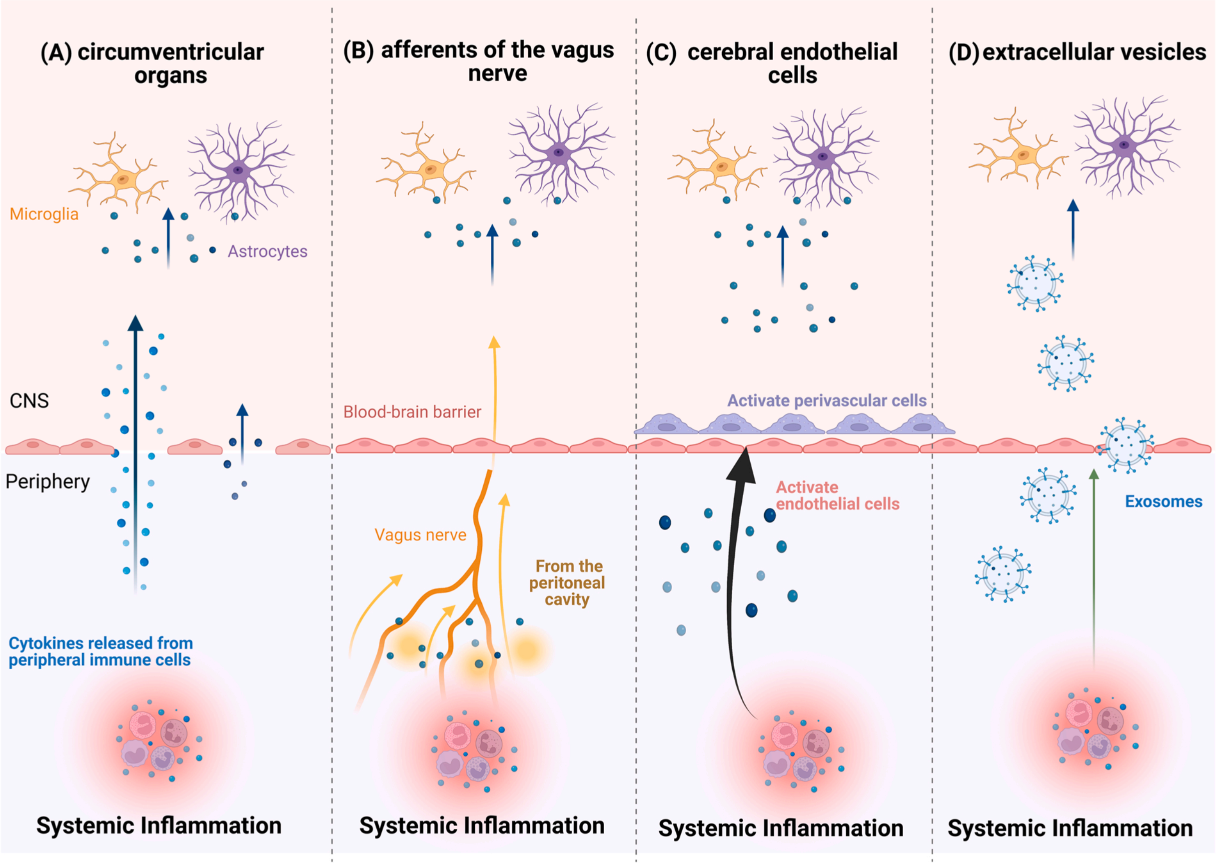

Fig. 4. Pathways of Communication Between the Periphery and the Central Nervous System. (A) The circumventricular organs are areas of the brain without an intact blood-brain barrier (BBB) where cytokines can diffuse through these areas into the brain parenchyma [30,99]. (B) The sensory afferent fibers of the vagus nerve provide direct means of communication from the peritoneal cavity to the brain stem [30]. (C) Activation of cerebral endothelial cells in an intact BBB signals the nearby perivascular cells in the parenchyma initiating communication with microglial cells in the CNS [30,99]. (D) The transport of cytokines across the intact BBB via transporters [73]. These transporters could include small extracellular vesicles such as exosomes. Created with BioRender.com.

as they are being delivered directly to the target cell rather than being dispersed in the solution [75].

3.2. Exosomes as RNA carriers

Based on environmental and inflammatory signals, the miRNA profile, gene expression, and the exosomal secretion of a cell can be regulated [78]. The possible roles of miRNAs include (1) targeting a gene's mRNA transcript for protein translation inhibition or protein degradation and (2) binding to toll-like receptors (TLRs) and inducing inflammation [9,79–81]. The profile of the exosomal miRNAs shows differences when compared between healthy controls and patients with either SCI or AD [82–84]. Exosomes, by being carriers of miRNAs and/or their target mRNAs, can contribute to the progression of these diseases by delivering them to distant cells [11,85]. If these exosomal miRNAs and pro-inflammatory cytokines spread to the CNS, they can influence downstream pathways and modify the brain's status and function [11, 85]. In patients with RA, the dysregulated miRNAs lead to the excess secretion of pro-inflammatory cytokines and autoantibodies and the activation of leukocytes [86]. A study has determined 14 miRNAs that are abnormally expressed and carried by exosomes in RA patients. In particular, exosomal miR-204–5p presented downregulated expressions in these patients [87]. Interestingly, miR-204–5p has also been deduced as a potent CSF exosomal miRNA with a downregulated expression in AD and frontotemporal dementia [88]. Research has also shown that the dysregulation of this miRNA could result in a cascade of symptomatic neurodegeneration and cognitive impairment [88,89]. The transfer of other dysregulated miRNAs from inflammatory microglia through exosomes can also contribute to synapses and cognitive impairment [90]. In addition, in another study, WT mice were injected intravenously with exosomes carrying short-interfering RNA (siRNA) targeting BACE1. The results showed a significant decrease in both mRNA and protein levels of BACE1. This study provides evidence for the crossing of exosomes from the periphery to the CNS and that exosomal content can influence genetic processes and downstream effects in neuronal and glial cells [91].

Other non-coding RNAs (ncRNA) can also be addressed; recent studies demonstrate long intergenic non-coding RNAs (lincRNAs) such as NEAT1, TUG1, MEG3, and XIST are carried by exosomes and are dysregulated in many diseases including NDDs and SCI diseases. The lincRNAs are about 200 nucleotides long and play essential roles in regulating cell homeostasis, development, and differentiation. A review gathered data from some experiments done on plasma, serum, mice models, brain tissue, cell models, etc., and showed that NEAT1 is found to be upregulated in AD, SLE, and RA, TUG1 is upregulated in both RA and AD and downregulated in SLE, MEG3 is downregulated in both RA and AD, and XIST is upregulated in RA and AD. XIST is also known to be correlated with BACE1 and Aβ_{1-42} [92]. These findings lend support to the claim that in diseased conditions, dysregulated miRNA and/or lincRNAs could be carried and spread via exosomes from the periphery to the CNS, hence offering a logical correlation between the similarity of expression patterns of these ncRNAs and the occurrence of the diseases.

3.3. Exosomes as neuroinflammation instigators

Various studies have demonstrated that exosomes promote inflammatory signaling in SCI diseases, especially in SLE and RA. In particular, in SLE, serum exosomes are found in much higher amounts in comparison with healthy patients, indicating that immune system imbalance and over-activation of immune cells can lead to increased secretion of exosomes. Also, these exosomes could induce the generation of pro-inflammatory cytokines, complement components, and immunoglobulin components in higher amounts compared to exosomes isolated from healthy patients [66]. In addition, exosomes derived from T-cells also showed the capability of activating various immune cells [93]. Other studies confirmed that exosomal miRNAs in SLE are also factors capable of interacting with TLRs and inducing pro-inflammatory cytokines production [79,80]. Thus, exosomes in SLE and possibly other SCI diseases can be considered "immunologically active" because they promote the peripheral inflammatory cascade [66]. Since further research has proven the capability of peripheral exosomes in traveling to the brain and delivering their contents [65,91], it can be proposed that through this mechanism, the cascade of neuroinflammation can become initiated. To support this claim, a study exhibited that when exosomes derived from the serum of LPS- administered mice and injected into C57BL/6J mice, they activated the microglia in the brain. Consequently, astrogliosis and an increase in the expression of pro-inflammatory cytokines and inflammation-related mRNAs and miRNAs in the CNS were seen in the recipient mice. Interestingly, it was also demonstrated that inflammatory miRNAs were found upregulated in the exosomes derived from the LPS-induced mice [94].

In the CNS, exosomes are potent mediators of the communication between the astrocytes and microglia by transferring the cytokines, miRNAs, and genetic information back and forth between the glial cells triggering oxidative stress and neuroinflammation [95], which are both actively seen in AD as triggers for tau hyperphosphorylation, Aβ pathogenesis, and irreversible neuronal dysfunction and degeneration [96,97]. Exosomes further propagate the neuroinflammation, rendering it chronic, by carrying and spreading Aβ, phosphorylated tau, presenilins, alpha-synuclein, and prion proteins from one region of the brain to the other [85,97–101]. Interestingly, a study also demonstrated that phosphorylated tau carried in exosomes is abundantly seen in CSF samples of early AD patients compared to late AD patients and non-AD patients [99]. This signifies that exosomal-mediated secretion of pro-inflammatory factors and aggregated and misfolded proteins is crucial in deepening AD progression. The whole picture indicates the presence of a "chicken and egg problem," meaning that the risk factors of neuroinflammation can also become consequences of itself, exhibiting the complex domino effect of neuroinflammation on the initiation and progression of AD through exosomes.

As exosomes are extensively involved in both peripheral and neuronal inflammatory processes, studies are exploring the usage of exosomes as diagnostic biomarkers and therapeutic vesicles. For RA-centered studies, exosomes were isolated from M2-type macrophages (macrophages that present anti-inflammatory and protective functions) and loaded with a plasmid DNA that encodes for IL-10, an anti-inflammatory cytokine, and a chemotherapeutic drug. When administered to mice models of RA, these exosomes were found at high concentrations around the joints that were inflamed and resulted in anti-inflammatory and therapeutic effects [102]. Other studies demonstrate the potential therapeutic role of exosomes derived from mesenchymal stem cells (MSCs) and dendritic cells. These cell types can transfer their immunosuppressive properties to the exosomes they secrete. Thus the administration of these exosomes can result in a regulatory effect on the adaptive and innate immune systems and aid in the tissue repair of the joint [103]. In another recent study, exosomes were isolated from MSCs, and their surfaces were metabolically glycoengineered to target the macrophages. Administrating these exosomes systemically in mice models of RA resulted in the accumulation of the exosomes at the inflamed joints, in which they promoted the polarization of M1 macrophages to the M2 phenotype, and triggered the release of anti-inflammatory cytokines (IL-4, IL-10). Hence these exosomes initiated the cascade of protective anti-inflammatory processes [104]. Since MSC-derived exosomes can reduce pro-inflammatory T cells and macrophages in the periphery; a study showed that exosomes can also reduce the number of reactive microglia in the CNS [105]. Thus, these exosomes are also being investigated as therapeutic agents in AD, illustrating that exosomes can be used for drug, miRNA, and enzyme delivery and for scavenging of toxic wastes to inhibit neuroinflammation and apoptosis and induce neuroprotective effects in the CNS [106].

4. Conclusion

Immunological responses and inflammatory diseases should be highly considered in the pathogenesis of NDDs. As portrayed in the literature presented, SCI diseases such as SLE and RA are often associated with high incidences of neurological disruption and cognitive dysfunction [5,26,85], putting the patient at higher risk for AD development. As SCI disorders can induce a state of chronic neuroinflammation in the brain, the proposed line of communication is via the release of exosomes. The claim that exosomes are the mediators of the pathological insults residing on the CNS from chronic systemic inflammations is very much in line with the rapidly growing and current research, which highlights the importance of exosomes in disease progression. Exosomes are dual-purpose players; by packaging, transporting, and signaling pathogenic and inflammatory molecules to distal and proximal cells, they can initiate numerous physiological and pathological responses. Depending on the exosomal content and exosomal surface proteins, the status of the cell and its extracellular environment are modified. In systemic and peripheral chronic inflammations, exosomes carry pro-inflammatory cytokines, complement proteins, and dysregulated non-coding RNAs, pass through the BBB, and spread these neurotoxic inflammatory molecules to glial and neuronal cells. Consequently, the integrity of the BBB is compromised, microglia switch their phenotypes from M2 to M1, and astrocytes become reactive; these changes result in an impaired migration, degradation, and phagocytosis of abnormal proteins, increased activation of APP-related secretases, down-regulation of tau phosphatases, and an increase in the levels of pro-inflammatory cytokines in the brain. The state of neuroinflammation also triggers synaptic loss, stimulates amyloidogenic β-amyloid generation and tau hyperphosphorylation, and further impairs amyloid-beta clearance capabilities. Exosomes also spread Aβ and tau pathologies to different brain regions, further deepening neuroinflammation and neurodegeneration. As for miRNAs, miRNAs involved with the regulation of mRNA transcripts, that are associated with AD-related genes, can be released by exosomes due to specific systemic and/or neuroinflammatory signals. Once delivered to neural and glial cells, they can affect the gene expression and function of the cell and its surroundings concerning AD pathology (Fig. 5). In the aging brain, these responses can be amplified, making the brain more susceptible. Thus, individually and collectively, they become significant risk factors for the initiation and progression of AD and possibly other NDDs.

As exosomes are potential mediators of the crosstalk between systemic inflammation and neuroinflammation, they can be utilized for therapeutic effects as mentioned above. For therapeutic purposes, it is essential to assess carefully (1) which exosomes to select (exosomes originating from which cell type, and which phenotype of that cell type, such as M2 or M1 microglia/macrophages), (2) which content to load the exosomes with, (3) which population of cells to target, and (4) which downstream pathways to impact. The current use of exosomes to prevent neuroinflammation and cognitive dysfunction upon a systemic inflammatory pathological insult is limited. However, if investigated, it could aid in preventing the brain of SCI patients from becoming susceptible to the initiation and development of AD and possibly other NDDs.

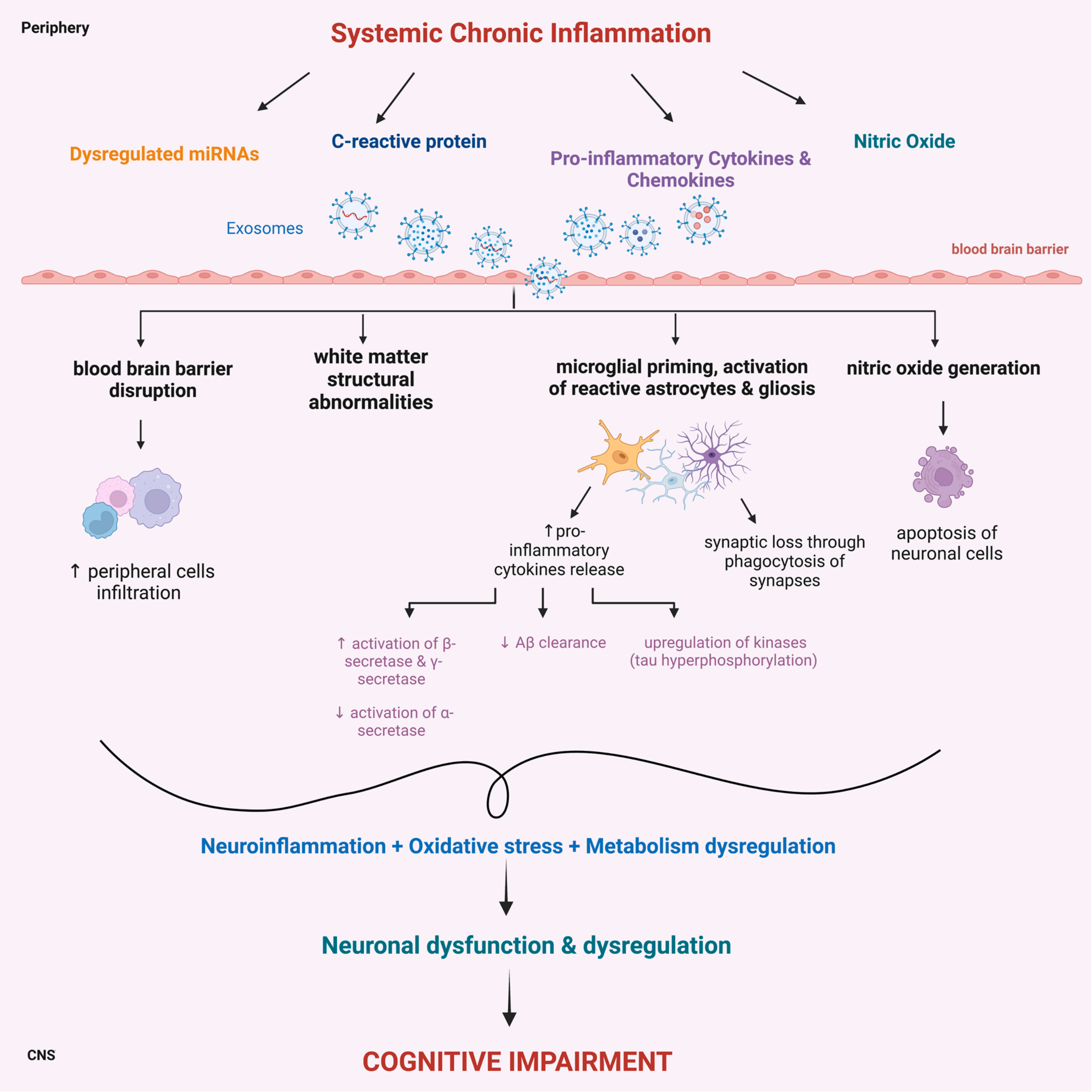

Fig. 5. The Proposed Role of Exosomes in Systemic Chronic Inflammation & Alzheimer's Disease. Schematic representation of exosomes carrying pro-inflammatory molecules in response to chronic systemic inflammation, crossing the blood-brain barrier and acting as mediators of the initiation and progression of Alzheimer's disease. Created with BioRender.com.

CRediT authorship contribution statement

Mehmet Ozansoy: Conceptualization, Writing – review & editing. **Houda Mikati:** Writing – original draft, Writing – review & editing, Investigation, Visualization. **Burak Yulug:** Supervision. **Halil Aziz Velioglu:** Supervision.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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