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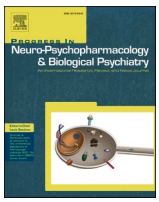

Microglia-derived sEV: Friend or foe in the pathogenesis of cognitive impairment

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ABSTRACT

As immune cells, microglia serve a dual role in cognition. Microglia-derived sEV actively contribute to the development of cognitive impairment by selectively targeting specific cells through various substances such as proteins, RNA, DNA, lipids, and metabolic waste. In recent years, there has been an increasing focus on understanding the pathogenesis and therapeutic potential of sEV. This comprehensive review summarizes the detrimental effects of M1 microglial sEV on pathogenic protein transport, neuroinflammation, disruption of the blood-brain barrier (BBB), neuronal death and synaptic dysfunction in relation to cognitive damage. Additionally, it highlights the beneficial effects of M2 microglia on alleviating cognitive impairment based on evidence from cellular experiments and animal studies. Furthermore, since microglial-secreted sEV can be found in cerebrospinal fluid or cross the BBB into plasma circulation, they play a crucial role in diagnosing cognitive impairment. However, using sEV as biomarkers is still at an experimental stage and requires further clinical validation. Future research should aim to explore the mechanisms underlying microglial involvement in various nervous system disorders to identify novel targets for clinical interventions.

1. Introduction

Cognitive impairment can arise as a consequence of neurologic, neurodegenerative, systemic, or psychiatric disorders that exert adverse effects on human cognitive processes, including thinking, learning, and memory abilities. Patients frequently manifest symptoms such as memory loss, confusion, and impaired judgment that significantly impede their daily functioning and occupational performance. Moreover, the substantial financial burden associated with this condition places immense strain on healthcare systems, society at large, and affected families (Wimo et al., 2023). As an integral component of the immune system, microglia crucially engage in cognition and homeostasis maintenance within the nervous system. Microglia exhibit distinct polarization states and play a crucial role in various neurological disorders, including neurodegenerative diseases, stroke, and traumatic brain injury. Improper activation of microglia may contribute to the pathogenesis and progression of central nervous system (CNS) disorders (Lu et al., 2022; Jin et al., 2023; Li et al., 2022a).

In recent years, small extracellular vesicles (sEV) have garnered significant attention due to advancements in intercellular communication research. These sEV contain diverse bioactive constituents including proteins, nucleic acids and metabolites, which can modulate neuronal signaling pathways and influence neurotransmission as well as oxidative stress responses (both pro-oxidation and antioxidation). Additionally, they can induce or counteract neuroinflammation while also promoting or inhibiting apoptosis. With increasing exploration into the impact of microglia-derived sEV on nervous system diseases, their potential applications in clinical treatment are emerging rapidly, thus regulating the secretion of these sEV has become a novel therapeutic strategy for addressing such conditions. This article provides a comprehensive review on the detrimental effects of M1 microglial sEV and the beneficial effects of M2 microglial sEV on cognitive impairment

Abbreviations: BBB, Blood-brain barrier; CNS, Central nervous system; EVs, Extracellular vesicles; sEVs, Small extracellular vesicles; m/lEV, Medium/Large extracellular vesicles; MVs, Microvesicles; AD, Alzheimer's disease; PD, Parkinson's disease; CSF, Cerebrospinal fluid; TBI, Traumatic brain injury; PUFA, Omega-3 polyunsaturated fatty acids; NGF, Nerve growth factor; ROS, Reactive oxygen species; Neu3, Neuraminidase-3; Trem2, Triggering receptor expressed on myeloid cells-2; DAM, Disease-associated microglial; VDBP, Vitamin D binding protein; MDD, Major depressive disorder; PET/CT, Positron emission tomography/CT; CBS, Cognitive behavioral syndrome; TENPO, Track-etched magnetic nanopore.

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based on evidence from cellular experiments, animal studies and clinical trials. We emphasize the progress of screening and isolation of microglia-derived sEV as biomarkers, aiming to offer new targets and perspectives for clinical intervention.

2. Impacts of microglial cells on cognitive impairment

2.1. Subtypes of microglia

Microglia can be classified into the following subtypes:

2.1.1. Homeostatic microglia

Homeostatic microglia are pivotal for maintaining basal cellular metabolism, homeostasis, and physiological functionality. These cells exhibit the expression of classical microglial markers, including Tmem119, P2ry12, Mtss1, and Cx3cr1 (Dadwal et al., 2024).

2.1.2. Disease-associated microglia (DAM)

DAM are predominantly linked to the late stages of diseases, indicating their progressive accumulation during disease progression. The activation of DAM is thought to be mediated by the triggering receptor expressed on myeloid cells-2 (Trem2)-associated signaling pathway, although initial activation may not be entirely Trem2-dependent, suggesting the involvement of additional regulatory factors (Rangaraju et al., 2018). DAM are further stratified into two primary functional subtypes:

2.1.2.1. Pro-inflammatory DAM. Representing M1-like microglia, this subtype undergoes classical activation and is characterized by the expression of genes such as Ptgs2, Il12b, Tlr2, and Hif1α. Pro-inflammatory DAM predominantly participate in inflammatory responses and immune signal transduction (Rangaraju et al., 2018; Krasemann et al., 2017).

2.1.2.2. Anti-inflammatory DAM. This subtype, also called alternatively activated or M2 macrophage phenotype, can be subdivided into three distinct states: M2a, M2b, and M2c. While these states share overlapping biochemical functions, they exhibit significant divergence in their activation stimuli, cytokine secretion profiles, and landmark expression (Wendimu et al., 2022). Anti-inflammatory DAM are characterized by the expression of genes such as Igf1, Dpp7, Apoe, Spp1, and Lpl, which are implicated in lipid metabolism, cholesterol efflux, antioxidative defense, aging/autophagy, and beta-amyloid (Aβ) clearance (Krasemann et al., 2017; Olah et al., 2020; Gerrits et al., 2021).

2.1.3. Transitional microglia

Transitional microglia represent an intermediary phenotype between homeostatic microglia and mature DAM. These cells express some of DAM-specific genes while concurrently exhibiting initial features of gene regulation. They are associated with early disease stages (Keren-Shaul et al., 2017).

2.1.4. Double-negative DAM subtype

This subtype demonstrates specific dynamic changes across various ages and disease stages, suggesting the existence of additional layers of complexity that remain incompletely elucidated (Keren-Shaul et al., 2017).

Microglia play a dual role in cognition, exerting both protective and detrimental effects. Recent studies have demonstrated the crucial role of microglia in maintaining myelin health during adulthood by regulating myelination processes and safeguarding myelin integrity. Alterations in myelin structure and damage are believed to contribute to early-stage dementia, while the loss of microglia leads to significant pathological changes such as excessive myelin growth, demyelination, and impaired neomyelination, ultimately resulting in cognitive impairment (McNamara et al., 2023). Moreover, microglia hold great significance in disease remission and treatment. Manipulating specific genes within microglia can effectively modulate their phagocytic function and enhance the clearance of neurotoxic substances, thereby improving memory behavior (Ennerfelt et al., 2022; Singh et al., 2022). Additionally, injecting microglia into the brains of mice with traumatic brain injury has been shown to facilitate nerve repair, promote regeneration, and effectively alleviate cognitive deficits caused by brain injury (Willis et al., 2020). Consequently, targeting microglia offers novel perspectives for treating nervous system diseases. Sustained activation of microglia, nevertheless, leads to progressive impairment of phagocytosis along with excessive secretion of proinflammatory factors that drive pathology development and cognitive decline (Wang et al., 2020; Gulen et al., 2023). Inhibiting microglial cells through inhibitors significantly reduces neuroinflammation levels (Henry et al., 2020). Peripheral inflammation can also induce persistent activation of central microglial reactivity followed by neural homeostasis disruption leading to long-term cognitive impairment (Leng et al., 2022). Suppressing excessive activation of microglia can mitigate central inflammatory responses; however, the precise mechanisms underlying this process remain unclear necessitating further investigation.

2.2. Heterogeneity of microglia

Microglia display significant heterogeneity across developmental stages, brain regions, and disease states, which is crucial for their roles in both physiological and pathological processes. What's more, sEVs derived from various sources of microglia exhibit distinct molecular profiles and biological properties (Murgoci et al., 2020).

2.2.1. Developmental stage heterogeneity

During embryogenesis, microglia adopt an amoeboid morphology, regulating neural progenitor cell numbers and neuronal fate. In early postnatal stages, they proliferate actively and engage in synaptic pruning. In adulthood, microglia assume a branched morphology, acting as immune cells to monitor brain homeostasis (Mosser et al., 2017).

2.2.2. Regional heterogeneity in the brain

Microglial density, morphology, molecular signatures, and function vary across brain regions.

2.2.2.1. Density. Microglial density differs significantly between brain regions and within layers of the same region. Recent studies indicate that local microglial density and molecular state are determined by the composition of pyramidal neuron subtypes. Additionally, microglial density varies by sex across regions such as the preoptic area, hippocampus, parietal cortex, and amygdala, both in steady-state conditions and under chronic stress (Stogsdill et al., 2022).

2.2.2.2. Morphology. Microglia are classified morphologically as ramified, primed, reactive, or amoeboid, with distinct structural features at each stage (Lier et al., 2021). Morphological heterogeneity is associated with disease, and distinct pathological mechanisms depend on their anatomical location (Simpson et al., 2007).

2.2.2.3. Molecular signature. Microglial expression profiles differ across brain regions. For instance, TREM-2 is expressed variably, regulating neuronal development and metabolic adaptation in a region-specific manner (Tagliatti et al., 2024).

2.2.2.4. Function. Microglial activation differs across distinct niches, influencing lesion types and pathogenesis (Basurco et al., 2023). For example, microglia in the inner plexiform layers are essential for cone-driven visual processing, as detected by electroretinography (Tagliatti et al., 2024) Recent studies have identified 1542 genes in microglia

linked to Alzheimer's disease (AD) stages, highlighting functional alterations (Sun et al., 2023). However, whether microglial functions are interchangeable within or across regions remains uncertain.

2.2.3. Sex-related heterogeneity

Microglia express estrogen and progesterone receptors, with sex-specific differences in function (Sierra et al., 2008). Microglia have been shown to exhibit distinct functional states in male and female mice subjected to identical antibiotic treatments, highlighting the influence of sex-specific factors on their responses (Shaik et al., 2023). Homozygous APOE4, the strongest genetic risk factor for AD, demonstrates greater sensitivity to sex hormones in females than males (Rosenzweig et al., 2024).

3. Mechanism of microglia-derived sEV in cognitive impairment

Extracellular vesicles (EVs) play a crucial role in mediating intercellular communication. EVs. However, the naming and definition of EVs have lacked standardization for an extended period. In accordance with the latest guidelines published in 2018, EVs are defined as lipid bilayer-enclosed particles released by cells, which lack the ability to self-replicate. Based on the diameter of the separated particles, small extracellular vesicles (sEVs) are typically characterized as <200 nm in diameter, while large extracellular vesicles (lEVs) are generally described as >200 nm In diameter. However, specific characterization method related to measured diameter require caution. In addition, the use of the biogenesis-related terms, ectosome and ectosome, are discouraged unless subcellular origin can be clearly demonstrated

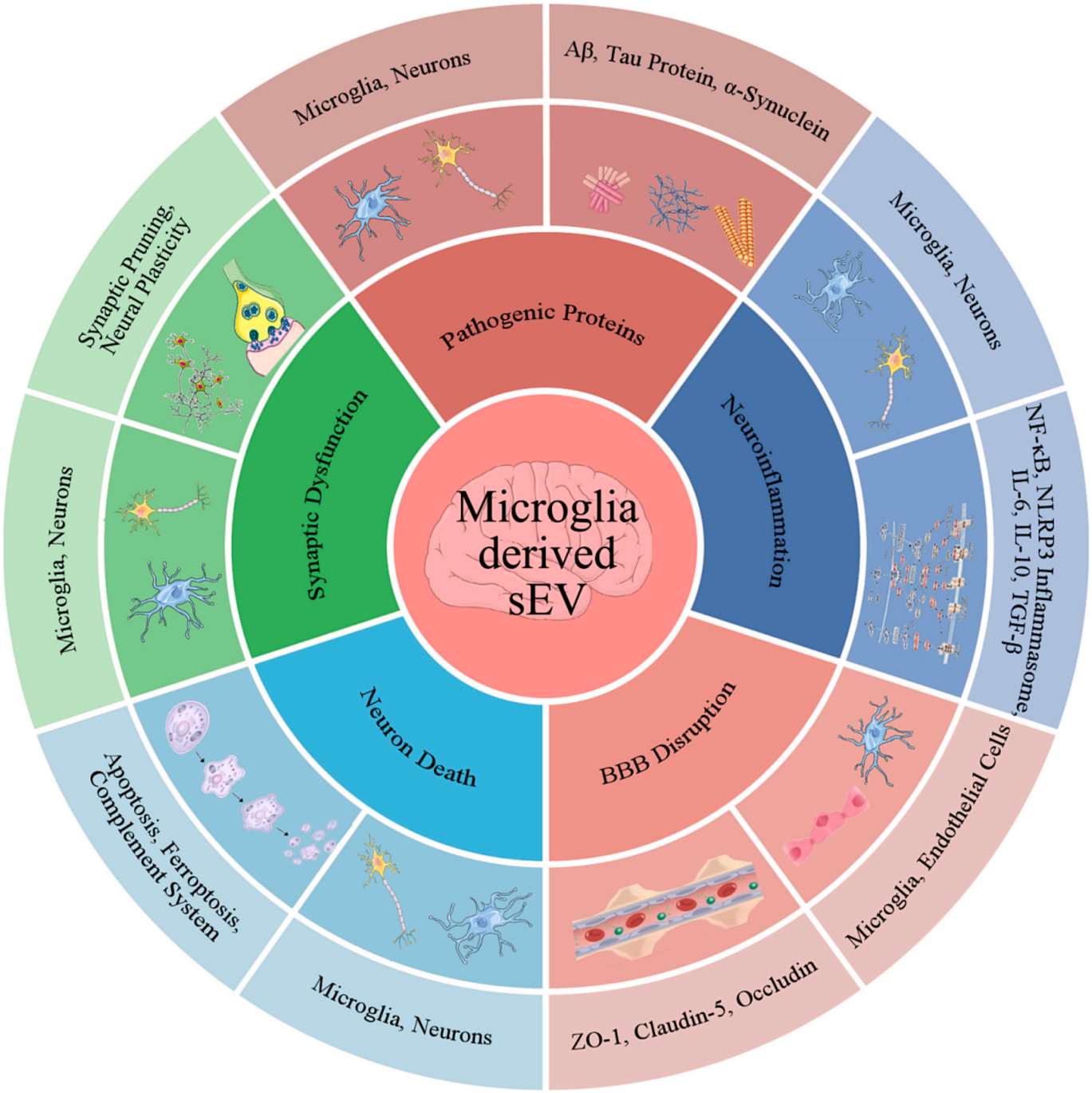

Fig. 1. Roles of microglia-derived sEV in cognitive impairment.

(Welsh et al., 2024). sEV are widely distributed in various body fluids such as blood, saliva urine, cerebrospinal fluid, and breast milk. They can communicate between cells through autocrine or paracrine signaling pathways, and also carry out long-range targeted transport to play biological roles in distant tissues via body fluids. Due to their rich contents, widespread distribution, and complex communication functions, the study of sEV has attracted great interest among scholars.

In CNS, neurons (Zhu et al., 2023), astrocytes (He et al., 2023), oligodendrocytes (Chamberlain et al., 2021), brain endothelial cells (Zhang et al., 2023a), and microglia are all capable of releasing sEV to regulate pathophysiological processes in the CNS. sEV derived from peripheral sources can also traverse the BBB into CNS through a membrane-dependent mechanism, targeting specific cells to modulate cognitive function (Wang et al., 2022a). Recent literature has increasingly emphasized the pathological and clinical advancements of sEV in relation to cognitive function. Given their crucial role in CNS homeostasis, this review primarily focuses on elucidating the mechanisms by which microglia-derived sEV contribute to cognitive impairment (Fig. 1).

3.1. Transmembrane transport of pathogenic proteins

Abnormally deposited proteins have been identified in the brains of patients with various neurodegenerative disorders, including AD and Parkinson's disease (PD). Numerous studies have demonstrated that sEV containing abnormal proteins can serve as biomarkers for neurodegenerative diseases (Si et al., 2023; Younas et al., 2022). Microglial dysfunction plays a significant pathological role in AD by contributing to plaque formation reduction when microglia are depleted (Spangenberg et al., 2019; Casali et al., 2020). Elevated levels of soluble Aβ and phosphorylated tau protein were observed in EVs isolated from blood, cerebrospinal fluid (CSF), and brain tissue of AD patients, suggesting the potential use of EV-derived biomarkers for AD diagnosis (Muraoka et al., 2020). Activated microglia secrete excessive sEV encapsulating phosphorylated tau protein which contributes to cognitive impairment through aggregation and diffusion (Zhu et al., 2022), exacerbating the progression of tau pathology alongside plaques (Clayton et al., 2021; Ruan et al., 2020). Inhibition of microglia significantly hinders tau propagation (Asai et al., 2015). In PD, transcellular transmission of α-syn via sEV can be internalized by neurons leading to their dysfunction and impaired cognition. Depletion of certain microglia populations results in a significant reduction in α-syn levels (Xia et al., 2019; Herman et al., 2023). Injection of sEV directly into the striatum induces phosphorylation and aggregation of α-syn along with degeneration of dopamine-producing neurons in multiple brain regions associated with the striatum, ultimately causing dyskinesia. Moreover, the combination of sEV with proinflammatory factors secreted by microglia exacerbates α-syn protein aggregation and diffusion in neurons, thereby intensifying neurotoxicity (Guo et al., 2020a). Furthermore, subsequent studies have revealed that microglia can also engulf sEV containing α-syn, triggering the activation of additional microglia (Xia et al., 2021).

Additionally, sEV can also exert beneficial effects. Trem2 is expressed on the sEV membrane of microglia and binds to Aβ in a Trem2-dependent manner, thereby facilitating the clearance of Aβ and ameliorating cognitive impairment in the early stages of AD (Huang et al., 2022). It's found that miR-711-carrying sEV derived from microglia, when injected into AD mice via tail vein, effectively targeted the inhibition of ITPKB, a protein kinase that promotes the formation of Aβ and tau protein (Stygelbout et al., 2014), while simultaneously increasing the M2/M1 ratio and alleviating cognitive dysfunction in AD mice (Zhang et al., 2020).

Currently, the majority of studies primarily focus on investigating the pathogenic mechanisms underlying abnormal transport proteins, with limited attention given to exploring their potential beneficial effects. Understanding the mechanism by which microglia sEV alleviate cognitive function could hold significant implications for mitigating neurodegenerative diseases, particularly during advanced stages.

3.2. Neuroinflammation

Upon treatment with LPS, the release of EVs from microglia was observed to increase. Analysis of these EVs revealed elevated levels of two proinflammatory cytokines, TNF and IL-6, indicating the presence of inflammatory cytokines in microglial sEV (Yang et al., 2018). Further investigations have demonstrated that sEV can activate other microglia through an autocrine pathway, thereby amplifying neuroinflammatory responses (Mallach et al., 2021). Moreover, under inflammatory conditions, microglia are stimulated to secrete a greater quantity of sEV (Delaveris et al., 2023). Consequently, sEV play a crucial role in facilitating the rapid spread of inflammation between cells. Reducing the number of sEV derived from microglia may potentially alleviate neuroinflammation.

During CNS infections, M1-secreted viral RNA is released outside the cell and transferred to neighboring cells upon activation, leading to increased production of brain interferon and numerous proinflammatory factors. This process mediates virus dissemination and sustained activation of nerve inflammation (Luong et al., 2021). Additionally, exposure to heavy metals like manganese can induce polarization and subsequent release of sEV by microglia. Notably, this promotes NLRP3 inflammasome activation as well as intercellular transmission. However, inhibiting sEV release significantly reduces proinflammatory factor levels and alleviates neuroinflammation (Franklin et al., 2014; Sarkar et al., 2019; Lucchini et al., 2023). These findings provide novel insights into the mechanisms underlying intercellular communication during neuroinflammation and cognitive impairment.

M1 microglia mediate neuroinflammation through excessive activation, resulting in the production of a plethora of proinflammatory factors. Conversely, M2 microglia exert anti-inflammatory effects and can stimulate various anti-inflammatory factors, such as IL-10 and TGF-β, to mitigate inflammation. For instance, elevated levels of miR-124-3p in microglial sEV following traumatic brain injury (TBI) can suppress neuronal inflammation and facilitate neurite outgrowth by transferring it to neurons (Huang et al., 2018). Importantly, it is believed that inflammation can be modulated by inducing a phenotypic switch. It's demonstrated that near-infrared light could induce microglial transition from an M1 phenotype to an M2 phenotype while ameliorating neuroinflammation through inhibition of the classical inflammatory signaling pathway NF-κB and regulation of endoplasmic reticulum stress via sEV containing anti-inflammatory miRNAs. This approach also safeguards synaptic plasticity and improves cognitive deficits in mice (Chen et al., 2023). Other studies have proved that microglial sEV could alleviate cognitive impairment induced by intermittent hypoxia through inhibition of NLRP3 inflammasome activity (Zhang et al., 2023b).

3.3. BBB damage

BBB acts as a protective barrier between the plasma and brain cells, regulating the movement of substances in and out of the brain to maintain a balanced brain environment. The integrity, permeability, and stability of BBB are crucial for cognition. Chronic inflammation can result in reduced blood flow and oxygen supply to white matter, leading to disruption of the extracellular matrix of vascular endothelial cells and increased permeability of BBB (Jalal et al., 2015; Gullotta et al., 2023).

Histologically, this disruption is characterized by the infiltration of proteins such as serum fibrinogen into parenchymal tissue (Roseborough et al., 2022). Previous studies have demonstrated that elevated levels of fibrinogen are associated with accelerated cognitive decline and mild cognitive impairment (Xu et al., 2008). Recently, a close association between fibrinogen was revealed to be released through sEV after priming NLRP3 inflammasome in microglia. Increased BBB permeability allows fibrinogen entry into brain tissue, triggering

microglial activation along with upregulation of NLRP3 expression and proinflammatory cytokines. This process disrupts tight junctions among endothelial cells within BBB. Simultaneously, microglia uptake fibrinogen and release sEV containing proinflammatory factors and fibrinogen itself further contributing to BBB breakdown while propagating inflammation through positive feedback mechanisms (Roseborough et al., 2023a). These findings highlight the relationship between microglial sEV-mediated BBB leakage and peripheral inflammation. Reducing fibrinogen levels following BBB damage has been shown to play a protective role against cognitive decline in AD (Ryu et al., 2009; Wen et al., 2023).

In addition, the disruption of key proteins of BBB was significantly associated with microglial sEV. It's discovered that exposure under HIV conditions to microglia-derived sEV containing the cofactor Nef, which was linked to HIV-induced cognitive impairment, resulted in reduced expression of the BBB tight junction protein ZO-1, thereby disrupting BBB integrity, permeability, and tight junctions. Furthermore, it induced the secretion of cytokines and chemokines from microglia (Raymond et al., 2016). The utilization of sEV inhibiting M1 microglia has also demonstrated alleviation of BBB disruption as well as neuronal apoptosis and death.

M2 microglial cells secrete substances externally that possess a neuroprotective effect during cerebral ischemia. In mice with cerebral infarction, intravenously injected sEV derived from M2 microglia increased the expression levels of key BBB proteins ZO-1, occludin and claudin-5 involved in regulating BBB integrity (Pan et al., 2023). Additionally, Omega-3 polyunsaturated fatty acids (PUFA) were employed to stimulate the secretion of microglial sEV containing nerve growth factor (NGF), which inhibited BBB destruction and neuronal death at traumatic brain injury sites (Lin et al., 2023). Therefore, M2 microglial cell-derived sEV offer novel insights into mitigating cognitive impairment by safeguarding BBB integrity.

3.4. Neuronal death

As a type of immune cells, microglia plays a crucial role in cell death processes such as neuronal apoptosis and ferroptosis. Stimulation of cells with sEV can modulate the expression levels of pro-apoptotic genes, including caspase 1 and caspase 8 (Van den Broek et al., 2020). Microglia-derived sEV were discovered to be capable of delivering complement proteins, thereby playing a significant role in neuronal apoptosis. Ethanol-induced stimulation of microglia leads to upregulation of C1q levels in sEV, resulting in increased deposition of neuronal C1q and activation of the downstream complement pathway, ultimately inducing neuronal apoptosis. Moreover, there is substantial accumulation of complement C1q at synapses in Tau mice and AD patients, which is associated with phosphorylated Tau and contributes to enhanced microglial phagocytosis as well as reduced synaptic density at synapses (Dejanovic et al., 2018). However, neutralization of C1q using specific antibodies rescues synaptic density while significantly reducing neuronal apoptosis (Dejanovic et al., 2018; Mukherjee et al., 2020). Furthermore, this study demonstrated that C1q bound to mitochondria through receptors that were linked to reactive oxygen species (ROS) production and oxidative stress. Co-culturing neurons with sEV secreted by M1 microglia resulted in significant downregulation of ferroptosis inhibitory protein within neurons along with a notable increase in lipid peroxidation levels—both characteristic features indicative of ferroptosis (Gao et al., 2022). Ferroptotic neuronal cells contribute to neuroinflammation by releasing inflammation-related factors and play an important role in cognitive impairment (Wang et al., 2022b; Wang et al., 2023a). In contrast, sEV derived from resting microglia do not induce ferroptosis in neurons. These findings suggested that targeting sEV derived from M1 microglia may represent a novel therapeutic approach for addressing cognitive impairment associated with ferroptosis.

Another study demonstrated that when vinpocetine was utilized to inhibit the activation of M1 microglia and promote the polarization of M2 phenotype, it effectively preserved the number and morphology of neurons (Zang et al., 2020). Therefore, regulating the polarization of M1 and M2 microglia holds significant importance in neuronal protection and alleviating cognitive impairment. Dai's study revealed that microglia-derived sEV encapsulating miRNA suppressed autophagy-related protein expression, resulting in a substantial reduction in neuronal autophagy after TBI and a notable improvement in cognitive function post-TBI (Li et al., 2019). Altered levels of miR-124-3p within microglial sEV from injured brains targeted the inhibitory transcription factor Rela, which was then transferred to hippocampal neurons to regulate the Rela/ApoE signaling pathway for mitigating neurodegeneration and enhancing cognitive outcomes following repetitive brain injury in AD (Ge et al., 2020). Other studies have corroborated similar findings (Ding et al., 2018; Liu et al., 2023; Song et al., 2019). Hence, microglia-derived sEV play a pivotal role in modulating nerve function and participating in neuroprotection.

3.5. Synaptic dysfunction

Microglia release EVs containing Aβ, which interact with neuronal nodes to undergo anterograde transport along the axon surface. This interaction leads to alterations in dendritic spine morphology and number at the site of contact with neurons, resulting in impaired long-term potentiation and memory deficits. Furthermore, these EVs contribute to the initiation and propagation of reduced synaptic plasticity during early stages of AD (Gabrielli et al., 2022). In a high-fat diet model, sEV released by inflammation-exposed microglia exert similar effects on dendritic spines by inhibiting synaptic stability and impairing dendritic spine formation. Thus, there is a link between inflammatory microglial sEV and excitatory synapse loss (Vinuesa et al., 2019). Under inflammatory conditions, microglia upregulate Neuraminidase-3 (Neu3) expression and modulate neuronal networks through secretion and transfer of sEV, providing a molecular mechanism for the contact-independent process of synaptic pruning (Delaveris et al., 2023).

Trem2 is associated with Aβ and tau pathology (Lee-Gosselin et al., 2023). In mice lacking Trem2, the propagation of tau encapsulated in sEV to the hippocampus was observed, leading to impaired synaptic function and decreased memory behavior (Zhu et al., 2022). Subsequent studies revealed that Trem2 plays a crucial role in microglia sEV function. Trem2 expressed on the sEV membrane of microglia can regulate sEV secretion without affecting their size. It's interesting to find that sEV bind to Aβ in a Trem2-dependent manner, thereby modulating the inflammatory environment surrounding Aβ and promoting its phagocytosis by microglia (Huang et al., 2022). Additionally, mutation of Trem2 in microglial cells resulted in increased secretion of DAM proteins linked to inflammation and diseases. Compared to the control group, these mutated cells exhibited significantly reduced abilities to promote neurite outgrowth and protect neurons (Mallach et al., 2021). Similarly, Zhu et al. reported that Trem2-deficient mice exhibited hippocampal memory and synaptic impairments, alongside elevated tau levels in microglial sEV, which promoted pathological tau trafficking, distribution, and seeding (Zhu et al., 2022). These findings underscored the pivotal role of Trem2 in microglial sEV, implicating its involvement in AD pathogenesis and progression through the regulation of Aβ and tau transport.

In contrast, sEV derived from M2 microglia have been shown to exert a protective effect on synapses against damage. For instance, in the case of TBI injury, microglia upregulated the synthesis and secretion of sEV under low body temperature conditions. These sEV were subsequently transferred to injured neurons where they released miRNA molecules that activated the PI3K-AKT pathway, promoting neurite outgrowth and facilitating synaptic recovery following TBI (Wang et al., 2023b). Similar findings were reported in Zhao's study (Zhao et al., 2021). Therefore, exploring strategies to effectively coordinate the secretion of sEV post-disease occurrence and enhance their role in mediating microglia-neuron interactions could potentially serve as a therapeutic approach for cognitive impairment resulting from synaptic damage.

4. Role of microglia-derived sEV in the diagnosis of cognitive impairment

In addition to the role as intercellular communicators, sEV released by microglia have the ability to traverse BBB and enter the peripheral bloodstream, thus enabling detection of centrally derived sEV in both CSF and plasma. The composition of sEV varies across different stages, making them potential novel biomarkers for disease diagnosis. For instance, microglia-derived sEV containing Vitamin D binding protein (VDBP) were found to be significantly reduced in the plasma of animal models with major depressive disorder (MDD). Their levels exhibited a negative correlation with VDBP levels in microglia within the limbic cortex and a positive correlation with VDBP levels in CSF. Therefore, they hold promise as potential candidate biomarkers for MDD diagnosis (Zhang et al., 2024). Furthermore, pathogenic proteins and nucleic acids encapsulated within plasma could also serve as biomarkers for nervous system diseases(Xia et al., 2019; Kumar et al., 2021; Arvanitaki et al., 2024). Due to the insidious onset of neurodegenerative disorders, diagnostic methods such as positron emission tomography/CT (PET/CT) and cognitive behavioral syndrome (CBS) are often delayed. The invasive nature of current examination biomarkers, particularly those obtained from CSF samples (Liu et al., 2022), further emphasize the non-invasive collection method offered by isolating sEV from various biological fluids including blood, urine, and saliva. Moreover, their stability in post-sample collection supports their utility in diagnosing related diseases (Duggan et al., 2022).

Detection of markers in blood can serve as a potent tool for early diagnosis of neurological disorders and assessment of microglial activity. Plasma-derived sEV enable non-invasive evaluation of microglial phenotype, while certain blood markers closely correlate with the extent of microglial activation. In contrast to other nerve cells, the lack of specific markers makes it challenging to accurately distinguish plasma microglia sEV from those derived from peripheral immune cells. A recent study proposed a novel antibody-based immunosequencing technique for individual EVs that enables multiple protein measurements within each sEV in order to facilitate the identification of the cellular origin of individual sEV when combined with existing CNS-EV enrichment methods (Ko et al., 2021). It's interesting to find that Tmem119, a more specific marker for microglia, has been utilized and considered a reliable indicator as its antibodies do not stain the infiltrated peripheral immune cells (Bennett et al., 2016). Additionally, although CD13 (Rohnert et al., 2012) and purinergic receptor P2ry12 (Zrzavy et al., 2017) are expressed in varying degrees by other cells or tissues, they can still serve as selective markers for microglia when distinguishing CNS cell-derived sEV.

By detecting these specific biomarkers indicating activated state-specific microglia in vitro, the functional status of microglia in patients can be comprehended, thereby providing a foundation for clinical diagnosis and treatment. Kumar et al. identified microglia-derived sEV from blood using the surface-specific marker Tmem119, uncovering distinct miRNA expression patterns associated with cognitive impairment severity (Kumar et al., 2023). Notably, miR-132-5p and miR-125b-5p demonstrated 100 % accuracy in distinguishing AD from cognitively normal individuals, while miR-29a-5p and miR-106b-5p effectively predicted broader cognitive impairments, including mild cognitive impairment (MCI), MCI-AD, and AD. As an early stage of AD, MCI does not invariably progress to AD. These miRNAs exhibited expression changes across disease stages, offering potential as biomarkers for early diagnosis, even during asymptomatic or minimally symptomatic phases, such as MCI, thereby extending the intervention window. In animal models of depression, miR-146a-5p was highly enriched in microglia, absent in hippocampal neurons, and minimally expressed in astrocytes (Jovicic et al., 2013). Elevated levels of miR-146a-5p in serum EVs were primarily mediated by microglia, with evidence showing its transfer to neurons via microglia-derived EVs, influencing neuronal stem cell proliferation and differentiation (Fan et al., 2022). These microglia-derived sEVs establish novel communication pathways between glial cells and neurons, presenting promising biomarkers and therapeutic targets for depression. Roseborough et al. further identified activated microglia-derived sEVs post-stroke, using Tmem119 and CD14 as markers. These EV biomarkers were detectable in plasma, with circulating microglial sEV levels significantly elevated 28 days after stroke (Roseborough et al., 2023b). In a preclinical stroke model, another study by this research team identified microglia-derived sEVs in circulation following BBB disruption. These sEVs encapsulated pro-inflammatory mediators and fibrinogen, facilitating the propagation of inflammatory signals and promoting collagen extravasation (Roseborough et al., 2023a). These findings underscored the pivotal role of microglia-derived sEVs in intercellular communication within the central nervous system. Their dynamic involvement in neuronal regulation and response to pathological states, such as depression and stroke, highlights their potential as diagnostic biomarkers and therapeutic targets. Future studies focusing on the mechanisms of sEV-mediated signaling may unlock new strategies for the early detection and treatment of neuropsychiatric and neurovascular disorders.

While microglia-derived sEVs hold significant promise as biomarkers, challenges remain: (1) **Specificity**: Distinguishing microglia-derived sEVs from the diverse sEV pool in plasma remains technically demanding (Roseborough et al., 2024). (2) **Standardization**: The lack of unified protocols for sEV isolation and analysis undermines reproducibility (Kumar et al., 2023). (3) **Clinical validation**: Current studies are largely preclinical, with limited sample sizes and insufficient depth of clinical validation (Roseborough et al., 2023b). Advancements in high-sensitivity detection technologies and the development of comprehensive biomarker databases will enhance the application of microglia-derived sEVs in neurological disease research. Future directions include precise identification of microglia-derived sEV biomarkers, investigation of dynamic sEV changes across disease stages and therapeutic interventions, and development of sEV-based diagnostic and treatment monitoring tools (Arvanitaki et al., 2024; Guo et al., 2020b; Li et al., 2022b).

Efficient isolation and analysis of sEV derived from specific regions of the CNS still pose significant challenges in current research. Therefore, optimizing the method for isolating sEV is crucial. Currently, commonly employed methods for the isolation of microglia-derived sEV include differential ultracentrifugation, Density gradient ultracentrifugation, Size exclusion chromatography, and so on (Table 1). Lemaire et al., isolated sEV from primary leech microglia cultures using ultracentrifugation combined with density gradient or size exclusion chromatography, and identified six miRNAs as potential signatures of these sEV through transcriptomics (Lemaire et al., 2019). Arab et al., compared differential ultracentrifugation with Optiprep™ density gradient ultracentrifugation and found that Optiprep™ could effectively eliminate contaminants and improve the quality of sEV analysis (Arab et al., 2019). Kumar et al. demonstrated the efficacy using a biotin-tagged antibody against the microglia-specific Tmem119 combined with streptavidin-coated magnetic beads (Kumar et al., 2021). While current sEV isolation methods show promise, issues like contamination and regional specificity persist. Future efforts should prioritize developing standardized, high-precision techniques to enhance purity and reproducibility.

Several novel techniques have been employed for the isolation of microglia-derived sEV and have demonstrated efficacy in isolating sEV from plasma. Kluge et al., utilized a seed amplification assay on blood samples from PD patients and observed signal amplification exclusively in the PD patient-derived sEV, providing a highly sensitive method to distinguish patients from healthy controls (Kluge et al., 2022). This represented the first application of a seed amplification assay on CNS-derived sEV which may also prove valuable in diagnosing other neurological disorders. Methods for screening biomarkers using omics techniques such as proteomics, transcriptomics, metabolomics, and lipidomics are gaining increasing attention (Dutta et al., 2023). For

Table 1
Common methods for isolating microglial derived sEV.

Isolation methods	Screening condition	Advantage	Disadvantage	Purity	References
Differential ultracentrifugation	Size; Density	Simple; Cheap; Gold standard	Time-consuming; Vulnerable to protein contamination; Structural damage	Low	(Zhu et al., 2022); (Liu et al., 2021); (Song et al., 2019)
Density gradient ultracentrifugation	Size; Density	Subpopulation isolation	Time-consuming Cumbersome operation Larger sample losses	High	(Arab et al., 2019); (Lemaire et al., 2019); (Cohn et al., 2021)
Precipitation-based methods	Solubility; Charge	Simple; Rapid; Commercial kits	Vulnerable to protein contamination	Low	(Mukherjee et al., 2020); (Luong et al., 2021); (Fan et al., 2019)
Size exclusion chromatography	Size; Molecular weight	Structural integrity; Subpopulation isolation	Vulnerable to protein contamination; Suitable for certain sEV	High	(Lemaire et al., 2019); (Van den Broek et al., 2020); (Murgoci et al., 2020)
Immunoaffinity-based techniques	Affinity	Subpopulation isolation	Expensive; Non-specific binding; Demands high specificity in marker selection	High	(Kumar et al., 2021); (Scaroni et al., 2022); (Ge et al., 2020)

instance, a nanofluidics device known as track-etched magnetic nanopore (TENPO) was developed for the classification of CNS-derived sEV (Ko et al., 2018). sEV isolation utilizing TEMPO in conjunction with off-chip RNA or protein biomarker analysis has been employed in mouse and human plasma and serum. These biomarkers can be combined through algorithms to accurately classify various injury states for TBI diagnosis and may also be utilized for biomarker analysis in patients with other neurodegenerative disorders (Ko et al., 2020). Nanoscale flow cytometry-based quantification of blood-derived sEV biomarkers has demonstrated the ability to differentiate between MCI and AD without the need for EV isolation, providing a rapid and efficient method that requires only minimal sample volumes (Dayarathna et al., 2024).

The isolation and characterization of sEV derived from specific CNS cells represent pivotal areas of ongoing research. It should be noted that the isolation process of sEV may, however, be influenced by factors such as sEV morphology, density, and surface antigen. Therefore, enhancing isolation purity while optimizing separation and detection methods are pressing issues. Additionally, the research and application of biomarkers still encounter numerous challenges. The detection methods and technologies with further optimization to enhance the accuracy and convenience of detection and large-scale multi-center clinical trials to validate sEV diagnostic value and therapeutic potential in clinical applications are significant in further study.

5. Summary and prospect

Microglia-derived sEV hold significant promise as therapeutic targets and foundational elements for the development of neuroprotective drugs and rehabilitation strategies. Although substantial progress has been made in elucidating the mechanisms of action of microglia-derived sEV in neurological disorders, their clinical application remains limited. Notably, inhibiting the formation, secretion, and transport of sEV has demonstrated potential in mitigating cognitive decline, highlighting their value as prospective targets for the prevention and treatment of cognitive impairment.

However, translating these findings into clinical practice faces considerable challenges. Current sEV isolation methods are hindered by limitations such as low efficiency and inadequate purity. Thus, the development of novel isolation and enrichment techniques is imperative to improve biomarker detection sensitivity and specificity. Furthermore, highly sensitive and accurate detection methods are needed to enable precise identification of sEV biomarkers, facilitating early diagnosis of cognitive impairment, monitoring treatment efficacy, and evaluating prognostic outcomes. Such advancements will provide essential support for clinical decision-making and the broader application of microglia-derived sEV in therapeutic interventions.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Authors' contribution

L-LC wrote the manuscript. WW approved and revised the final manuscript. All authors have read and approved the final manuscript.

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Lilin Chen: Writing – review & editing. **Wei Wang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

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Data availability

The data supporting the conclusion of this article is included within the "References" section.

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