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REVIEW PAPER

Bidirectional Communication Between the Brain and Other Organs: The Role of Extracellular Vesicles

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Abstract

A number of substances released by the brain under physiological and pathological conditions exert effects on other organs. In turn, substances produced primarily by organs such as bone marrow, adipose tissue, or the heart may have an impact on the metabolism and function and metabolism of the healthy and diseased brain. Despite a mounting amount of evidence supports such bidirectional communication between the brain and other organs, research on the function of molecular mediators carried by extracellular vesicles (EVs) is in the early stages. In addition to being able to target or reach practically any organ, EVs have the ability to cross the blood–brain barrier to transport a range of substances (lipids, peptides, proteins, and nucleic acids) to recipient cells, exerting biological effects. Here, we review the function of EVs in bidirectional communication between the brain and other organs. In a small number of cases, the role has been explicitly proven; yet, in most cases, it relies on indirect evidence from EVs in cell culture or animal models. There is a dearth of research currently available on the function of EVs-carrying mediators in the bidirectional communication between the brain and bone marrow, adipose tissue, liver, heart, lungs, and gut. Therefore, more studies are needed to determine how EVs facilitate communication between the brain and other organs.

Keywords Brain · Bidirectional communication · Exosomes · Extracellular vesicles · Microvesicles

Introduction

In 2007, McEwen (McEwen 2007) suggested the existence of bidirectional communication between the brain and the cardiovascular, immunological, and other systems, in which neurological and endocrine processes are key players. Since the brain is a primary regulator of the neuroendocrine, autonomic, immunological, and behavioral systems (McEwen 2006), peripheral organ stimulation may also have direct and indirect effects on brain function. However, little is known of the bidirectional communication between the brain and other organs. Brain factors are involved in the regulation of other organs throughout the body, and many have yet to be identified (Wang et al., 2022a). Meanwhile, substances produced or released primarily by organs such as the heart, bone marrow, or adipose tissue may affect normal or abnormal brain function and metabolism (Letra & Santana 2017; Rigueira et al. 2021). A typical example of a myokine expressed simultaneously in cardiac muscle and brain is irisin, a protective factor with antioxidant, anti-inflammatory, and anti-apoptotic effects (Li et al. 2021b). It has been suggested

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that increased expression of soluble epoxide hydrolases in the brain and liver may play a role in the pathogenesis of major psychiatric disorders, further indicating the importance of cross-talk between brain and liver in major psychiatric disorders (Zhang et al. 2020). Redistribution of local perfusion and pulmonary intravascular microthrombus might cause the increase of alveolar dead space and depletion of pulmonary surfactants due to excessive stimulation of sympathetic never, which may completely disrupt the regulatory mechanisms of ventilation and perfusion balance and cause hypoxemia after TBI (Pelosi et al. 2005). Qualitative differences in gut bacterial composition are linked to mood and behavioral impairment, and exposure to particular non-pathogenic bacteria can modulate brain chemistry and behavior in adult animal (Bravo et al. 2011) and change depression and anxiety-like symptoms in human subjects (Nikolova et al. 2019; Bajaj et al. 2019).

To further increase the complexity of this interaction network, studies published in the last decade have identified a large number of intra- and inter-organ signals mediated by EVs. Almost all types of cells, including those found in brain tissue, have the ability to produce EVs (Gabrielli et al. 2022; Karnati et al. 2019; Ruan et al. 2021). EV-mediated intercellular communication in the brain has been reviewed. The neuron-to-glial cell ratio is 1:10; thus, the former must communicate with neighboring glial cells. This continuous communication ensures homeostasis within the brain. EVs have a significant impact on the central nervous system (CNS) of the brain's information flow, which is a complicated, highly regulated process. Moreover, EVs could be produced, released, and absorbed by neurons (Durur et al. 2022; Huang et al. 2018a; Nogueras-Ortiz et al. 2020) and glial cells (Bakhti et al. 2011; Datta et al. 2020; Li et al. 2021c; Lombardi et al. 2019; Pei et al. 2019; Wang et al. 2011) under both normal and pathological conditions. Substantial numbers of proteins and nucleic acids are present in EVs, and when these materials are transferred to other cells, they may have an impact on biological processes. The cargo of EVs is determined during their biogenesis and by the stimuli affecting the parental cells (Jiang et al. 2022). For example, hypoxic stimulation of neurons and glial cells can cause changes in the size, number, and expression of EVs cargo (Jiang et al. 2022).

Recently, there have been a growing amount of studies on the intercommunication between brain and other organs because EVs can function across the BBB, but there is still no complete review article that extensively discusses the body of knowledge on signals between the brain and other organs carried by EVs. Here, we review the role of EVs in communication between the brain and other organs. Their role has been clearly demonstrated in a few cases; however, in most cases, it has been based on indirect evidence from EVs in cell culture or animal models.

Extracellular Vesicles: Biogenesis and Function

A highly heterogeneous membranous structure that originates from different parental cells, Evs can be classified into three subtypes based on biogenesis, size, composition, and load: exosomes, microvesicles (MVs), and apoptotic vesicles (van Niel et al. 2018; Zhang et al. 2021a, b). Despite trying to further classify EVs based on their size, origin or function, the primary overlap of these characteristics does not clearly distinguish them. Thus, the consensus recommendation of the International Society for Extracellular Vesicles (ISEV) is to use "extracellular vesicles" as a "general term for particles naturally released from cells separated by lipid bilayers that cannot be replicated, i.e., do not contain a functional nucleus (Witwer & Thery 2019)" and we will use this term in this review; nevertheless, in some cases, we will cite the same terminology used by the authors in their article.

The size and genesis of EVs vary widely. EVs range in size from 30 to 5000 nm (Karpman et al. 2017), with exosome diameters ranging from 30 to 150 nm (Rai et al. 2021; Yang et al. 2020) and MVs ranging from 100 to 1000 nm (Kailashiya 2018; Laberge et al. 2018). Apoptotic bodies generally have a diameter of up to 5000 nm (Atkin-Smith et al. 2015). Exosomes are intraluminal vesicles that are intermediates in the endosomal system that are released when multivesicular bodies fuse with the cell surface. They are created by the inward budding of endosomal membranes during the maturation of multivesicular bodies (van Niel et al. 2018; Villarroya-Beltri et al. 2016). In order to release exosomes, several cellular steps need to be accomplished: first, a cup-shaped structure composed of cell surface proteins and hydrophilic proteins forms the first invagination. This leads to the generation of early endosomes (Lloyd et al. 2002). Second, the endosomal limiting membrane invaginates inward to produce multivesicular bodies containing intraluminal vesicles, i.e., the future exosomes (Heijnen et al. 1999). The process ends with degradation of the multivesicular contents by lysosomes or autophagosomes or fusion with the plasma membrane and release of intraluminal vesicles as exosomes (van Niel et al. 2018; Villarroya-Beltri et al. 2016). Exosome secretion has now spread to a wider variety of cell types, and its importance in intercellular communication in both healthy and pathological conditions is well recognized (Colombo et al. 2014) (Fig. 1A).

Different from exosomes, MV formation and release are the result of a complex process of cytoskeletal reorganization and loss of physiological asymmetry in the membrane bilayer (Hugel et al. 2005). Those MVs were produced by the outward budding and fission of the plasma

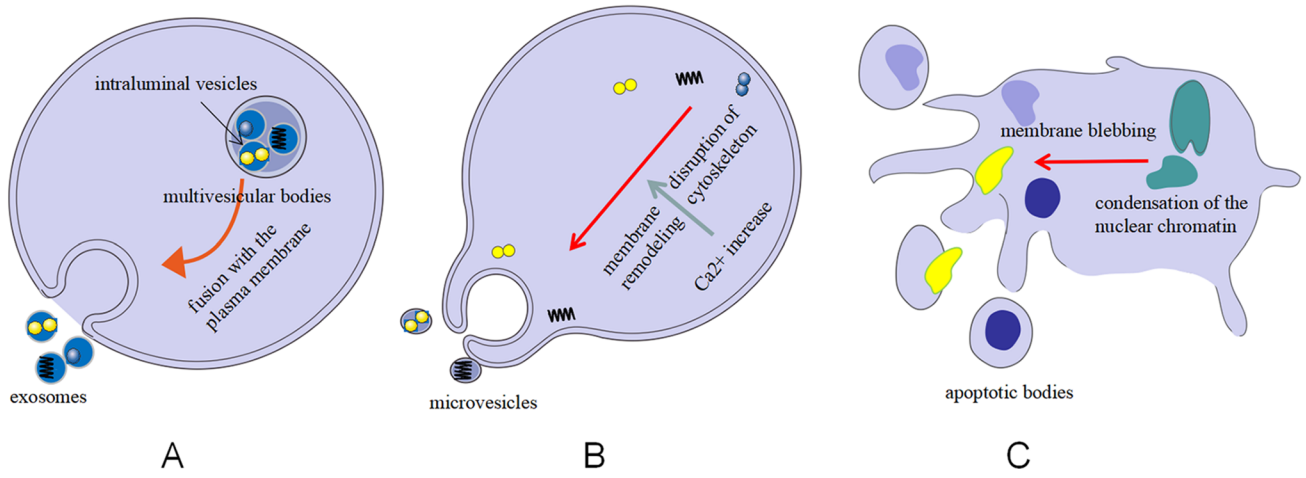

Fig. 1 Schematic diagram of the process of EVs production. **A** To release exosomes, a cup-shaped structure composed of cell surface proteins and hydrophilic proteins forms the first invagination. This leads to the generation of early endosomes. Second, the endosomal limiting membrane invaginates inward to produce multivesicular bodies containing intraluminal vesicles. When the multivesicular bodies fuse with the plasma membrane and empty their contents, intraluminal vesicles are released and are termed exosomes once they are extracellulars. **B** Microvesicle formation is calcium-dependent and associated with loss of membrane asymmetry and disruption of the cellular cytoskeleton. **C** Apoptosis undergoes several stages, beginning with condensation of nuclear chromatin, followed by membrane blistering, and progressing to disintegration of cell contents into distinct membrane-encapsulated vesicles called apoptotic vesicles or apoptotic vesicles. *EVs* extracellular vesicles; *MVs* microvesicles

membrane, followed by the release of vesicles into the extracellular space. The process depends on an increase in cytosolic Ca^{2+}, which activates enzymes, leading to depolymerization of the actin cytoskeletal depolymerization and outward bending of the cell membrane (Comfurius et al. 1990; Kelton et al. 1992; Piccin et al. 2007). When cells are activated, the increased cytosolic calcium activates flippase (which allows lipids to move toward the outer membrane) and scramblase (which moves lipids in both directions), and flippase (which allows lipids to move toward the inner membrane) is inactivated, causing negatively charged phosphatidylserine to flip to the outer leaflet of the phospholipid bilayer. This facilitates membrane budding and the formation of microvesicles (Turturici et al. 2014). The budding process is accomplished by contracting the cytoskeletal structure through actin–myosin interactions (McConnell et al. 2009; Muralidharan-Chari et al. 2009) (Fig. 1B).

Cellular apoptosis consists of these major stages, beginning with condensation of nuclear chromatin, next, membrane blistering and disintegration of cell contents into apoptotic bodies (Kerr et al. 1972) (Fig. 1C). Although exosomes and MVs are secreted during regular cellular processes, apoptotic bodies are exclusively produced during planned cell death. By specifically interacting with the recognition receptors on the phagocytes and the particular alterations in the structure of the apoptotic cell membrane, macrophages can remove apoptotic substances by phagocytosis. The most characteristic of these changes is the translocation of phosphatidylserines to the outer leaflets of the lipid layer. These translocated phosphatidylserines bind to membrane associate protein V recognized by phagocytes (Ishibe et al. 1975). Another well-characterized membrane change involves the oxidation of surface molecules. These changes create sites for the binding of thrombospondin (Savill 1997; Friedl et al. 2002) or complement protein C3b (Takizawa et al. 1996). As a result, C3b and coagulation-responsive proteins are successively acknowledged as three well-known indicators of apoptotic bodies. However, little is known of their function in cell–cell interactions (Battistelli and Falcieri 2020; Elmore 2007; Erwig and Henson 2008).

EVs are important for transmitting information in lipids, nucleic acids, proteins (polypeptides, enzymes, cytokines, etc.), and so on (van Niel et al. 2018). Recently, EV proteins and nucleic acids as potential biomarkers or therapeutic targets for diseases have been attracting extensive attention (Beard et al. 2021; Forro et al. 2021; Karnati et al. 2019; Ko et al. 2020), but EV lipids have received little attention (Su et al. 2021). Overall, EV composition depends mainly on the condition of the parental cell and can change according to physiological or pathological conditions (*e.g.*, inflammation and stress) (Guedes et al. 2020; Valadi et al. 2007).

EV-mediated Bidirectional Communication Between the Brain and Other Organs

The bidirectional communication between the brain and other organs is thought to be mediated by EVs. EVs can cross the BBB to transport lipids, peptides, proteins, and nucleic acids and can reach and target almost any organ (Banks et al. 2020a). Determining the source of EVs is challenging. As far as I know, brain-specific EVs have not yet been discovered so far. However, as we have discussed before, the levels and carriers of EVs are different under different physiopathological conditions. Because EV content depends on the state of the parent cell, it may be easier to understand its origin under pathological conditions. Peraza et al. (Delgado-Peraza et al. 2021) found that Astrocytic EVs showed significant amounts of complement, which is linked to Alzheimer's disease (AD), and circulating neuronal EVs had high quantities of tau and β-amyloid protein (Aβ), suggesting their potential as liquid biopsies for neurological illnesses. Nevertheless, it is possible to identify the origin of EVs under physiological conditions based on the characteristics of cell-specific protein cargo, which is also a direction for future development. Of these, the contents elaborated below are summarized in Table 1 and Fig. 2.

EVs in Brain–Bone Marrow Crosstalk

The effectiveness of bone marrow mesenchymal stem cells (BMSCs) in the treatment of central nervous system diseases has been a closely investigated and controversial issue. Transplanted BMSCs can promote neural repair by assuming a functional neuronal and glial cell phenotype (Li and Zhang et al. 2021a, b; Maltman et al. 2011). However, mesenchymal stem cells may function primarily in a paracrine manner rather than intracellularly (Phinney & Pittenger 2017). BMSC-derived exosomes (BMSC-exos) have therapeutic potential because of their stable biology, low immunogenicity, and ability to cross the BBB and localize to the injured area (Phinney and Pittenger 2017). These findings promote the study of exosomes released from BMSCs and their protective and repairing effects in the brain. Liu et al. (Liu et al. 2021) reported a reduction in brain infarct size and alleviation of short-term neurobehavioral deficits in rat by BMSC-exos-mediated switching of microglia between the M1 and M2 phenotypes. Hypoxic BMSC-exos rescue oxygen glucose deprivation (OGD)-induced neuronal damage by inhibiting nod-like receptor family pyrin domain-containing 3 (NLRP3)-containing inflammasome-mediated pyroptosis in vitro (Kang et al. 2021). Based on their ability to transmit information, the functions of non-coding RNA in exosomes have been investigated (Zhang et al. 2015). BMSC-exos enriched in miR-124 reduce proinflammatory microglia activation, protect BBB integrity, and ameliorate stroke-mediated injury, possibly in a manner involving peroxiredoxin 1 (PRDX1) (Tian et al. 2022b). MiR-124-3p is downregulated in rats with hypoxic–ischemic brain damage (HIBD), but its upregulation by BMSC-exos improves neurological function, attenuates neuronal pathology and structural damage to neurons, inhibits oxidative stress, and lowers neuronal apoptosis in HIBD rats by inhibiting tumor necrosis factor receptor-associated factor 6 (TRAF6) (Min et al. 2022). Lipocalin 2 (LCN2) is expressed at high levels and is also a target gene for miR-138-5p. MiR-138-5p derived from BMSC-exos attenuates neurological impairment by targeting LCN2 to promote astrocyte proliferation and suppress inflammatory responses after ischemic stroke (Deng et al. 2019). In addition, BMSC-exos ameliorate cerebral infarction by transferring miR-23a-3p, thereby inducing microglia inactivation and M2 polarization (Dong et al. 2022). By targeting the histone deacetylase 4 (HDAC4)/B-cell lymphoma 2 (Bcl-2) axis to prevent hippocampus neuronal death, miR-93 delivered by BMSC-derived EVs (BMSC-EVs) improves HIBD (Shi et al. 2022). BMSC-exos carrying the long non-coding RNA ZFAS1 suppress oxidative stress and inflammation associated with ischemic stroke (Yang and Chen 2022). MiR-410 delivered by BMSC-EVs targets HDAC4 and prevents brain damage in hypoxic–ischemic mice (Shen et al. 2022). The downregulation of phosphatase and tensin homologs, which led to the activation of the PI3K/protein kinase B/rapamycin mechanistic target/glycogen synthase kinase-3 beta signaling pathway, may be partially responsible for the improvement in neural plasticity and recovery after stroke after intravenous administration of miR-17-92 cluster-enriched BMSC-exos. (Xin et al. 2017). In addition, another study found that intravenous delivery of miR-17-92 cluster-enriched BMSC exosomes after traumatic brain injury (TBI) dramatically decreased neuroinflammation and neuronal cell death and boosted neurogenesis and angiogenesis (Zhang et al. 2021b). The BMSC-exos hsa-miR-23b-3p inhibits intracranial aneurysm formation by targeting krueppel-like factor 5 (KLF5) via inhibition of the PI3k/AKT/NF-κB signaling pathway (Sun et al. 2020). BMSC-EVs have therapeutic potential for brain dysfunction and exert a neuroprotective effect after subarachnoid hemorrhage (SAH) (Han et al. 2021). The development of SAH is related to endothelial cell damage and BBB breakdown. BMSC-EVs can deliver non-coding RNA KLF3-AS1 to brain microvascular endothelial cells, thereby attenuating neurological deficits after SAH by promoting cell viability and inhibiting apoptosis (Cheng et al. 2022).

Table 1 EVs-mediated communication between brain and other organs

EV cargo	Source organ	Recipient organ	Disease or disease model	Functions and mechanisms	Source of EVs
Group1					
Unknown	Bone morrow	Brain	In vivo:MCAO; In vitro:OGD/R	Ameliorate cerebral injury via suppression of NLRP3 inflammasome-mediated inflammation and pyroptosis by modulating microglial polarization.	BMSCs
Unknown	Bone morrow	Brain	In vitro:OGD	Have significant neuroprotective effects against NLRP3 inflammasome-mediated pyroptosis	BMSCs
MiR-126	Bone morrow	Brain	In vivo:MACO In vitro:OGD/R	Reduce microglia activation and protect the integrity of the BBB and reduce the extent of stroke-mediated injury	BMSCs
MiR-124-3p	Bone morrow	Brain	In vivo:HIBD	Alleviate neuron pathological and structural damages, suppressed oxidative stress and reduced neuronal apoptosis	MiR-124-3p-modified BMSCs-Exos
MiR-138-5p	Bone morrow	Brain	In vivo:MCAO; In vitro:OGD	Promote proliferation and inhibit inflammatory responses of astrocytes	BMSCs
MiR-23a-3p	Bone morrow	Brain	In vivo:MACO	Induce the deactivation of microglia and M2 polarization	BMSCs
MiR-93	Bone morrow	Brain	In vivo:MCAO; In vitro:OGD	Suppress hippocampal neuron apoptosis through targeting the HDAC4/Bcl-2 axis	BMSCs
ZFAS1	Bone morrow	Brain	In vivo:MCAO; In vitro:OGD/R	Curb oxidative stress and inflammation related to ischemic stroke	BMSCs overexpressing ZFAS1
MiR-410	Bone morrow	Brain	In vivo:HIBD	Attenuate apoptosis by inactivating the Wnt pathway via targeting HDAC4.	BMSCs transfected with the mimic of miR-410
MiR-17-92 cluster	Bone morrow	Brain	In vivo:TBI and MCAO	Reduce neuroinflammation and enhance endogenous angiogenesis and neurogenesis Increases neural plasticity	Human BMSCs transfected with a miR-17-92 cluster plasmid
Hsa-miR-23b-3p	Bone morrow	Brain	In vivo:basilar artery aneurysm	Inhibite IA formation by targeting KLF5 through suppression of the PI3k/Akt/NF-κB signaling pathway	Human BMSCs
Unknown	Bone morrow	Brain	In vivo: SAH	Inhibite NF-κB and activated AMPK to reduce inflammation	BMSCs
KLF3-AS1	Bone morrow	Brain	In vivo: SAH	Attenuate neurological deficits and endothelial dysfunction	KLF3-AS1-containing BMSCS-EVs
MiR-129-5p	Bone morrow	Brain	In vivo: SAH	Anti-inflammation and antiapoptosis effects through quenching the activity of HMGB1-TLR4 pathway	BMSCs
MiR-21	Bone morrow	Brain	In vivo:transgenic APP/PS1 mice	Restore synaptic dysfunction and modulate inflammatory responses	hypoxia-preconditioned BMSCs

Table 1 (continued)

EV cargo	Source organ	Recipient organ	Disease or disease model	Functions and mechanisms	Source of EVs
Unknown	Bone morrow	Brain	In vitro: AβOs add to hippocampal neurons	Protect neurons against AβO-induced oxidative stress and synapse damage	BMSCs
MiR-29c-3p	Bone morrow	Brain	In vivo: injection of Aβ1-42 In vitro:AD hippocampal neurons	Decrease Aβ deposition area and Aβ plaques; increased neuron viability and reduced apoptosis rate	BMSCs
MiR-1224	Brain	Bone	In vivo:TBI	Enhance the colony forming ability and osteoclast differentiation efficacy and activated NF-κB signaling genes in bone marrow-derived cells	BMSCs
Group 2					
Brain repair function proteins	Adipose	Brain	In vivo:subcortical stroke	Improve axonal sprouting, tract connectivity, remyelination and oligodendrogenesis	ADSCs
MiR-126	Adipose	Brain	In vivo:ischemic stroke	A decrease of neuron cell death and an increase of cell proliferation	ADSCs
MiR-30d-5p	Adipose	Brain	In vivo:MCAO; In vitro:OGD	Suppress autophagy and promote M2 microglia/macrophage polarization	miR-30d-5p-overexpressing ADSCs
Circ-Rps5	Adipose	Brain	In vivo:MCAO	Decrease neuronal damage and shift microglia from an M1 to M2 phenotype	Hypoxic pre-treated ADSCs
MiR-31	Adipose	Brain	In vivo:MCAO; In vitro:OGD	Reduce neuronal damage	ADSCs
MiR-181b-5p	Adipose	Brain	In vivo:MCAO; In vitro:OGD	Promote the angiogenesis of brain microvascular endothelial cells via miR-181b-5p/TRPM7 axis	ADSCs
PEDF	Adipose	Brain	In vivo:MCAO; In vitro:OGD	Activate autophagy and suppress neuronal apoptosis	PEDF modified ADSCs
MiR-9-3p	Adipose	Brain	In vivo:cognitive impairment associated with insulin resistance	Induce remarkable synaptic loss and cognitive impairment	ADSCs
NEP	Adipose	Brain	In vitro:a neuroblastoma cell line N2a cells genetically modified to overproduce human Aβ	Decrease both secreted and intracellular Aβ levels in the N2a cells	ADSCs
Group 3					
TNF-α	Liver	Brain	In vivo:Hyperammonemia	Induce glial activation, neuroinflammation and enhance GABAergic neurotransmission	Plasma of hyperammonemic rats
ApoE4	Liver	Brain	In vivo: ageing-associated hypothyroidism	Activated NLRP3 inflammasome by increasing cholesterol level in neural cells	Liver
Unknown	Liver	Brain	In vivo:hepatic ischemia reperfusion injury	Activate NLRP3 inflammasome and caspase-1-dependent pyroptosis in the hippocampus and cortex	Serum of hepatic ischemia reperfusion injury

Table 1 (continued)

EV cargo	Source organ	Recipient organ	Disease or disease model	Functions and mechanisms	Source of EVs
Group 4					
MiR-126?	Brain	Heart	In vivo:Ischemic stroke	Maintainvascular integrity and regulate angiogenesis	Circulating blood of ischemic stroke
MiR-1 MiR-27a	Heart	Brain	In vivo:myocardial infarction	Inhibite synaptic vesicles exocytosis; reduces the levels of SNAP-25 protein levels in the hippocampu	Overexpression of miR-1 in the heart
MiR-28a MiR-34a	Heart	Brain	In vivo:chronic heart failure	Enhance the inflammatory response of RVLM, which further promote sympathetic hyperactivity	Heart from rats with chronic HF
CircRNAs?	Brain	Heart	In vivo:TBI	Might be related to myocardial contraction and calcium signalling pathways	The brain extracellular space in mice with TBI
Group 5					
TFs	Brain	Lung	In vivo:TBI	May be an initiator of coagulation activation	Brain
Inflammasome	Brain	Lung	In vivo:TBI	Activate the pulmonary inflammasome and promote acute lung injury	Circulating blood after TBI
ASC	Brain	Lung	presente lung injury after TBI	Activatethe inflammasome and resulted in endothelial cell pyroptosis	Serum in patients presenting with lung injury after TBI
Caspase-1	Lung	Brain	In vivo:VILI	Cause neuroinflammation with microglial activation and activation of caspase-1 and caspase-1/gasdermin D in the brain	Plasma of VILI
Transcription factors	Lung	Brain	SARS-CoV-2-infected lung	Influence the neuronal gene regulatory network and accelerate neurodegeneration.	SARS-CoV-2- infected lung
Group 6					
Unknown	Gut	Brain	No	Increase the permeability of the BBB and promote the activation of astrocytes and microglia, inducing an inflammatory response and tau hyperphosphorylation	Gut microbiota
Unknown	Gut	Brain	Elderly people and aged mice	Suppress NF-κB-mediated BDNF expression in the hippocampus, resulting in cognitive impairment.	*Paenalcaligenes hominis*
exRNAs	Gut	Brain	monocyte-specific live CX3CR1-GFP mice	Cause neuroinflammation	*Periodontopathogen Aggregatibacter actinomycetemcomitans*
exRNAs	Gut	Brain	No	The production of TNF-α via the TLR-8 and NF-κB signaling pathways.	*Aggregatibacter actinomycetemcomitans*
GABA α-ketoglutarate ? glutamate	Gut	Brain	No	Unknown	*toxigenic B. fragilis*

Table 1 (continued)

EV cargo	Source organ	Recipient organ	Disease or disease model	Functions and mechanisms	Source of EVs
Unknown	Gut	Brain	Chronic restraint stress	Rescue the reduced expression of BDNF, and blocked stress-induced depressive-like behaviors	*Lactobacillus plantarum*
Unknown	Gut	Brain	Chronic restraint stress	Restore stress-induced expression of MeCP2, Sirt1, and/or neurotrophic factors in the hippocampus	*Bacillus subtilis* and *probiotic Akkermansia muciniphila*
GABA	Gut	Brain	No	activated neurite extension in neuronal cells(SH-SY5Y)	GABA-treated intestinal epithelial cells
MiR-130?	Gut	Brain	No	Increased BBB permeability	Adherent-invasive *E.coli*- infected IECs
MHC-II?	Gut	Brain	No	Response to neuroinflammation and brain injury and changes in neurogenesis and plasticit	IECs
Unknown	Gut	Brain	Sepsis-associated encephalopathy	Cause M1 polarization in MLNs and the accumulation of circulating IL-1β. Circulating IL-1β promoted the damage and apoptosis of neurons	Intestinal flora disturbance induced the exosome release of IECs

ADSCs Adipose-derived stem cells; *ApoE4* Apolipoprotein E4; *ASC* Apoptosis-associated speckled protein; *Aβ* β-Amyloid protein; *BAB* Blood–air barrier; *BBB* Blood–brain barrier; *Bcl-2* B-cell lymphoma 2; *BDNF* Brain-derived neurotrophic factor; *BMSCs* Bone marrow mesenchymal stem cells; *BMSCs-exos* BMSCs-derived exosomes; *BMSCs-EVs* BMSCs-derived EVs; *EVs* Extracellular vesicles; *exRNAs* Extracellular RNAs; *GABA* Gamma-Aminobutyric acid; *HF* Heart failure; *HDAC4* Histone deacetylase 4; *HIBD* Hypoxic–ischemic brain damage; *HMGB1* High mobility group box 1; *IECs* Intestinal epithelial cells; *KLF5* krueppel-like factor 5; *LCN2* Lipocalin 2; *MHC-II* Major histocompatibility complex II; *miR* MicroRNA; *MS* Multiple sclerosis; *NEP* Neprilysin; *NLRP3* NOD-like receptor family pyrin domain-containing 3; *OGD* Oxygen-glucose deprivation; *PEDF* Pigment epithelium-derived factor; *RVLM* Rostral ventrolateral medulla; *SAH* Subarachnoid hemorrhage; *SARS-CoV* Severe acute respiratory syndrome coronavirus; *TBI* Traumatic brain injury; *TFs* Tissue factors; *TLR4* Toll-like receptor 4; *VILI* ventilation-induced lung injury

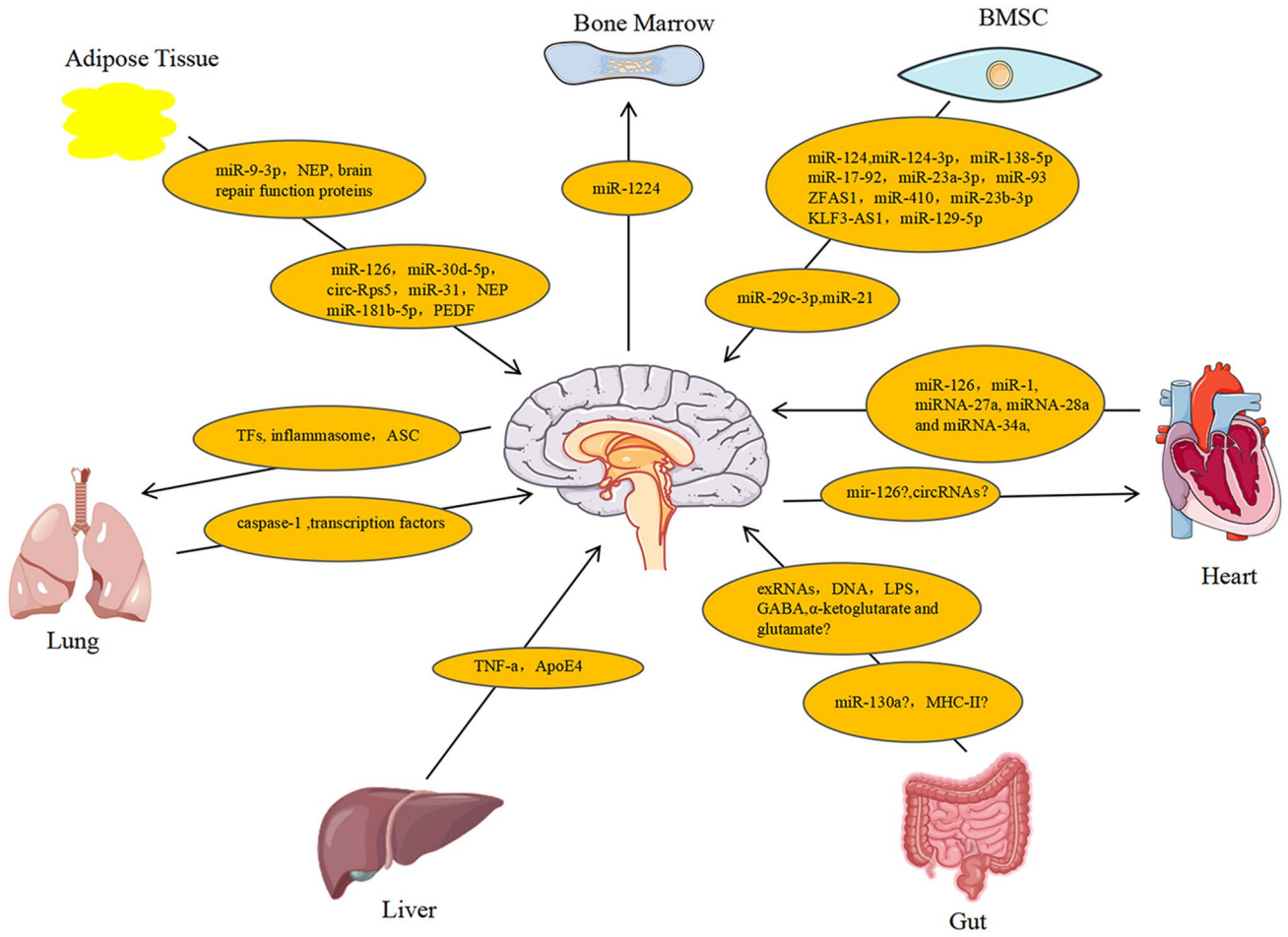

Fig. 2 Extracellular vesicle-carried substances mediate communication between the brain and other organs. *BMSC* bone marrow mesenchymal stem cell; *TF* Tissue factor, *ASC* apoptosis-associated speckled protein; *ApoE4* Apolipoprotein E4, *PDEF* pigment epithelium-derived factor, *LPS* Lipopolysaccharide; *NEP* neprilysin; *GABA* gamma-Aminobutyric acid; *exRNA* extracellular RNA; *MHC-II* major histocompatibility complex II

Xiong et al. (Xiong et al. 2020) also showed that miR-129-5p from BMSC-exos ameliorates early brain injury after SAH by inhibiting the anti-apoptotic and anti-inflammatory effects of the high mobility group box 1 (HMGB1)/toll-like receptor 4 (TLR4) pathway.

BMSC-EVs are also important in chronic degenerative diseases. Many chronic neurodegenerative diseases, including multiple sclerosis and AD, are associated with demyelination. Demyelination is caused by damaged myelin sheaths, and additional damage to demyelinated axons can be caused by inflammatory responses, oxidative stress, mitochondrial dysfunction, ion channel dysfunction, and excessive excitatory neurotransmitter release (like glutamate) (Dendrou et al. 2015; Schattling et al. 2019; You et al. 2019). EVs enhance myelin maintenance by minimizing oligodendrocyte DNA damage and boosting the expression of myelin-related gene expression and raising the proportion of actively myelinating oligodendrocytes in aged rhesus monkeys (Go et al. 2021). Also, BMSC-exos promote remyelination by acting directly on oligodendrocyte progenitor cells and indirectly on microglia in the demyelinated CNS (Go et al. 2021). Lateral ventricular administration of BMSC-exos improves AD-like behavior in mice by modulating hippocampal glial activation and its associated neuroinflammatory and brain-derived neurotrophic factor (BDNF)-related neuropathological changes (Liu et al. 2022). BMSC-EVs have beneficial effects in AD mouse models, possibly via inhibition of Aβ-induced inducible nitric oxide synthase (iNOS) expression (Elia et al. 2019). BMSC-EVs exert anti-inflammatory effects by modulating cytokine release (Cui et al. 2018; de Godoy et al. 2018), inhibiting iNOS, or preventing Aβ-oligomer toxicity (Wang et al. 2018).

Meanwhile, Cui et al. (Cui et al. 2018) reported that exosomes from hypoxia-preconditioned BMSCs increase the miR-21 level in the brain of AD mice. Furthermore, miR-21 supplementation reversed cognitive impairments and

avoided degenerative characteristics in APP/PS1 mice. Sha et al. (Sha et al. 2021) further highlighted that the Wnt/β-catenin pathway is crucial, and that BMSCs-EVs deliver miR-29c-3p to hippocampal neurons to reduce Aβ and inflammatory cytokines to improve AD.

Chronic inflammatory activation in the blood and brain is increased after TBI, including mobilization of bone marrow-derived immune cells (Braun et al. 2018, 2017; Ma et al. 2017; Wang et al. 2017). Therefore, TBI may create a chronic proinflammatory environment in bone marrow, leading to progressive bone loss. Interestingly, EVs may mediate signaling from the brain to bone marrow. Bone marrow-derived EVs from TBI mice increase osteoclast differentiation and colony formation (Singleton et al. 2019). MiR-1224 may mediate TBI-dependent NF-κB activation and bone marrow osteoblast differentiation (Singleton et al. 2019). However, further studies are needed to assess whether EVs in bone marrow after TBI are released locally or transported from the site of injury.

EVs in Brain–Adipose Tissue Crosstalk

The largest endocrine organ, adipose tissue produces a variety of biologically active mediators that work with peripheral organs and the CNS (Hajer et al. 2008; Scherer 2019). Adipokines released from adipose tissue modulate neuroinflammation and oxidative stress, two major pathophysiological and physiological processes in the CNS, and are linked to central nervous system diseases. A significant source of circulating non-coding RNAs, many of which are transported by exosomes, is adipose tissue (Thomou et al. 2017). Thomou et al. (Thomou et al. 2017) suggested that adipose tissue is the source of the majority of circulating exosomes. There is proof that exosomes can mediate communication between the brain and adipose tissue. Otero-Ortega et al. claim that axonal sprouting and development, oligodendrocyte creation, tract connection, and remyelination after subcortical ischemic stroke are all mediated by exosomes of adipose origin (Otero-Ortega et al. 2017). A proteomic analysis of EVs identified more than 2000 proteins associated with brain repair, which if used therapeutically, may improve functional recovery (Otero-Ortega et al. 2017). Adipose tissue contains adipose-derived stem cells (ADSCs), an important source of EVs. Geng et al. (Geng et al. 2019) demonstrated that miR-126-rich ADSC-derived exosomes (ADSC-exos) alleviate ischemic stroke by inhibiting ischemic stroke-induced microglia activation and inflammatory responses and promoting neurogenesis and functional recovery. ADSC-exos rich in miR-30d-5p protect against acute ischemic stroke by inhibiting autophagy-mediated microglia/macrophage polarization to suppress inflammatory responses and reduce the area of infarcted brain damage (Jiang et al. 2018). Moreover, exosomes from hypoxia-pretreated ADSCs lessen brain damage brought by acute ischemic stroke and encourage M2 microglia/macrophage polarization by delivering the non-coding RNA circ-Rps5 (Yang et al. 2022). In addition, Lv et al. (Lv et al. 2021) proposed other molecular participants involved in EV-mediated signaling among adipose tissue and neurons. Exosome-carried miR-31 targeted neurons and downregulated TRAF6, thereby upregulating interferon regulatory factor 5 (IRF5) and ameliorating ischemic stroke-induced neuronal damage (Lv et al. 2021). ADSC-exos protect neurons from damage by suppressing the NF-κB and mitogen-activated protein kinase (MAPK) pathways and preventing microglia activation (Feng et al. 2019). ADSC-exos protect neurons from damage by suppressing the NF-κB and mitogen-activated protein kinase (MAPK) pathways and preventing microglia activation (Huang et al. 2018b). Ischemic hypoxia is associated with angiogenesis or the formation of new microvessels in pre-existing vessels. The induction of cerebral angiogenesis is critical for promoting post-stroke functional recovery (Ruan et al. 2015). In vitro, ADSCs-Exos enhance the angiogenesis of brain microvascular endothelial cells after OGD via miR-181b-5p, revealing a novel role for ADSCs-exos in stroke (Yang et al. 2018).

The relationship between cognitive impairment and ADSC-exos has also been studied. Such exosomes promote cognitive impairment via synaptic loss and chronic neuroinflammation, thereby facilitating the progression of cognitive impairment in high-fat diet-fed rats. Also, suppression of miR-9-3p may prevent insulin resistance cognitive impairment associated with obesity (Wang et al. 2022b). AD is characterized by the accumulation of Aβ in the brain due to an imbalance between Aβ production and clearance. ADSC-exos carrying enzymatically active neprilysin are transferred to N2a cells, a neuronal cell line with Aβ overexpression, where they reduce the extracellular and intracellular levels of Aβ40 and Aβ42. This has therapeutic potential for AD (Katsuda et al. 2013). In vitro, ADSC-exos modulate the cellular phenotype of amyotrophic lateral sclerosis (ALS), including superoxide dismutase (SOD-1) aggregation and mitochondrial dysfunction, suggesting therapeutic potential for ALS (Lee et al. 2016). Therefore, ADSC-exos may promote restoration of brain function, and their therapeutic potential warrants further investigation.

EVs in Brain–Liver Crosstalk

Hepatic encephalopathy demonstrates the close relationship between the brain and the liver (Cabrera-Pastor et al. 2019; Felipo 2013). The average incidence of neurological complications after liver transplantation is about 20% (Bronster et al. 2000). Hyperammonemia is the main cause of neurological impairment in patients with cirrhotic hepatic

encephalopathy. Individuals with liver cirrhosis present with persistent hyperammonemia, which induces moderate hepatic encephalopathy, which causes motor incoordination and mild cognitive and motor impairment (Balzano et al. 2020; Cabrera-Pastor et al. 2019). Chronic hyperammonemic rats experience these neurological changes, which cause cerebellar and hippocampal neuroinflammation, altered GABAergic and glutamatergic neurotransmission, and motor incoordination and cognitive impairment (Cabrera-Pastor et al. 2019). EVs are thought to be involved in the transfer of peripheral changes to the brain. Plasma EVs in hyperammonemic rats were changed and the TNF-α level was elevated. When injected into normal rats, EVs from plasma of hyperammonemic rats reached the cerebellum and caused changes in Purkinje neurons and microglia in particular particularly Purkinje neurons and microglia, further resulting in neuroinflammation and motor incoordination (Izquierdo-Altarejos et al. 2022). Also, elevated TNF-α levels in EVs from hyperammonemic rats' blood activate the TNF receptor 1 (TNFR1)/C–C motif chemokine ligand 2 (CCL2)/BDNF/tropomyosin receptor kinase B (TrkB)/KCC2 and TNFR1/NF-kB/glutaminase/GABA transporter 3 (GAT3) pathways, thereby enhancing cerebellar GABAergic neurotransmission. As a result, microglia activation, increased GABAergic neurotransmission, and motor incoordination occur (Izquierdo-Altarejos et al. 2022). Apolipoprotein E4 (ApoE4) alleles are strongly associated with age-related cognitive impairment and AD (Kanekiyo et al. 2014; Strittmatter et al. 1993). Age-related thyroid deficiency can enhance exosomal transport of ApoE4 from liver to brain, which causes AD-related dementia and neuronal dysfunction in ApoE4 allele carriers. These changes also coincide with ApoE4-induced activation of the NLRP3 inflammasome and pyroptosis of neurons (Zhang et al. 2022a, b). Exosomes isolated from serum of rats with hepatic ischemia–reperfusion injury may induce neuronal damage in the hippocampus and cortex, which is associated with the NLRP3 inflammasome and caspase-1-dependent pyroptosis (Zhang et al. 2019). Although there have been fewer studies on the function of EVs in communication between brain and liver under normal and pathological conditions, this is an interesting area for future study.

EVs in Brain–Heart Crosstalk

There are numerous bidirectional connections between the cardiovascular system and CNS. Indeed, 11–18% of stroke patients suffer symptomatic heart failure, and the prevalence of left ventricular systolic dysfunction is 24% (Doehner et al. 2018). Stroke patients often present with myocardial injury, ischemic-like electrocardiographic changes, and arrhythmias (Ay et al. 2006; Oppenheimer 1994; Tokgozoglu et al. 1999). In preclinical studies, an elevated plasma catecholamine level after ischemic stroke is positively associated with the incidences of myocardial lesions and cardiac injury (Meloux et al. 2018). Despite knowledge gaps in our understanding of the processes of brain–heart relationships, emerging evidence suggests that EVs and their cargo might act as mediators of both inter-organ and intercellular interactions (Venkat et al. 2018). Under physiological conditions, EVs can cross the BBB (Banks et al. 2020b), and their ability to do so is enhanced by damage to the BBB (Dickens et al. 2017). Indeed, EVs produced from the brain under healthy or diseased settings can interact, and some of the molecular mechanisms and signaling pathways are similar in myocardial infarction (MI) and stroke (Otero-Ortega et al. 2020). Circulating EVs from patients with MI and stroke have comparable protein and miRNA profiles, despite the fact that they are two distinct clinical diseases affecting various organs and cell types (Otero-Ortega et al. 2020). Patients who have suffered an ischemic stroke, a cerebral hemorrhage stroke, or a SAH have higher circulating EV levels; this is linked to a poor prognosis (Huang et al. 2009; Lackner et al. 2010). Blood-derived MVs promote the produce of the endothelial cell cytokine IL-6 (Mesri and Altieri 1999), the expression of which is linked to the development of vasospasm (Schoch et al. 2007). IL-6 can induce vasospasm in the peripheral vasculature, including the cardiac vessels, leading to coronary syndrome. In cerebral hemorrhage, plasma procoagulant microvesicles levels are also significantly elevated and are linked to stroke development (Huang et al. 2009). Platelet MVs also play an important role in the communication between the brain and the heart. Altered platelet activity caused by platelets and/or MVs produced by the injured brain can lead to thromboembolic events and associated cardiac complications after brain injury (Horn et al. 2016). In preclinical studies, EVs produced by the heart entered the brain via blood and induced sympathetic activation in a rat model of chronic heart failure (Tian et al. 2022a). Also, plasma EVs from rats with chronic heart failure enhanced the inflammatory response in the rostral ventrolateral medulla (RVLM), possibly promoting sympathetic hyperactivity (Tian et al. 2022a). Moreover, cardiac-derived exosomes from mice with MI not only attenuated extracellular secretion of hippocampal synaptic vesicles after crossing the BBB but also led to hippocampal microtubule loss, which was improved by the exosomes production inhibitor GW4869 (Sun et al. 2018).

The non-coding RNAs are prevalent in EVs and have been linked to cardiac and brain dysfunction (Zheng et al. 2021). Long et al. (Long et al. 2013) reported that miR-126 carried by exosomes in circulating blood was decreased significantly for at least 24 weeks in patients with ischemic stroke, which may affect other organs including the heart. Endothelial cell-specific MiR-126 is essential for maintaining vascular integrity and controlling angiogenesis (Wang

et al. 2008). Heart failure, atrial fibrillation, coronary artery disease, and possibly severe stroke-induced heart problems may be associated with a miR-126 deficiency (Qiang et al. 2013; Wang et al. 2008). Mesenchymal stem cell-derived EV-carried miR-17–92 cluster is a key regulator of cardiomyocyte proliferation in the neonatal and adult heart, as well as of post-stroke neural progenitor cell proliferation (Chen et al. 2013; Zhang et al. 2021b). In addition, the miR-17-92 cluster protects the ischemic heart and brain by targeting phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinases/extracellular signal-regulated kinase signaling pathways (Zhou et al. 2013). MiR-1 is specifically expressed in adult cardiac, and an elevated serum miR-1 level after MI suggests cardiomyocyte necrosis as its source (Chistiakov et al. 2016). MI-induced overexpression of miR-1 in blood and brain may be associated with exosomes released from the heart, which enter the brain and are taken up by hippocampal neurons, resulting in hippocampal neuronal microtubule damage and reduced microtubule protein polymerization (Duan et al. 2018). These changes are prevented by inhibitors of exosome production and by selective inhibition of miR-1. Also, overexpression of miR-1 in the heart in a mouse model of MI suppressed the extracellular secretion of synaptic vesicles. This is caused by exosome-mediated transport from the heart to the brain induced by an elevated miR-1 level in the hippocampus, inhibiting synaptosomal-associated protein, 25 kDa (Snap25) expression (Duan et al. 2018). In a chronic HF rat model, cardiac-derived EVs enriched in miRNA-27a, miRNA-28a, and miRNA-34a entered the RVLM through the BBB to inhibit the nuclear factor-erythroid factor 2-related factor 2 (Nrf2)/antioxidant signaling pathway and promote sympathetic hyperactivity (Tian et al. 2022a).

Using high-throughput whole transcriptome sequencing of TBI mice with Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analyses, Zhao et al. (Zhao et al. 2018) showed circRNAs were predicted to influence myocardial contraction and calcium signaling pathways (Zhao et al. 2018). Although these findings are preliminary, they may provide an important basis for future research on exosomes carrying circRNAs in brain–heart communication.

EVs in Brain–Lung Crosstalk

The blood level of EV is markedly elevated in the acute phase of TBI in mice (Morel et al. 2008). Moreover, other neurological conditions like ischemic stroke and cerebral hemorrhagic stroke have higher levels of circulating EV (Chen et al. 2017). Tissue factors (TFs) are abundant on the EV surface and have procoagulant and proinflammatory effects following TBI. TFs initiate the coagulation reaction by activating thrombin to form fibrin (Grover and Mackman 2018). After TBI, the disrupted BBB allows EVs from injured brain tissue to enter the peripheral circulation, where they induce coagulation, fibrinolysis, vascular fibrin deposition, and thrombosis (Zhao et al. 2016). Circulating EVs are primarily consumed by the lung (Takahashi et al. 2013). Hideki et al. (Yasui et al. 2016) showed that brain-derived MVs expressed TFs in the alveoli and that thrombin inhibitors reduced lung injury, suggesting a role for brain-derived MVs in TBI-induced acute lung injury (ALI). After craniocerebral injury, injured brain tissue releases large amounts of damage-associated molecular patterns (DAMPs), triggering an innate immune response (Shi et al. 2019). EVs are implicated in the development of ALI as mediators of inflammation. For instance, EVs containing proinflammatory cytokines were released after experimental TBI and taken up by lung cells, triggering inflammatory vesicle activation. Kerr et al. (Kerr et al. 2018) found that EVs containing inflammasome proteins caused ALI in a TBI mouse model, and detected caspase-1, apoptosis-associated speck-like protein (ASC), and IL-18 in pulmonary type II alveolar epithelial cells. Enoxaparin, a blocker of EVs, significantly ameliorated ALI, implicating EVs in brain–lung communication. An inflammasome component in EVs, ASC, which contains a caspase recruitment domain, promotes TBI-induced lung injury. Targeting of human lung microvascular endothelial cells by EVs from TBI subjects induces inflammasome activation, leading to pyroptosis (Kerr et al. 2019). The lungs facilitate gas exchange through the alveolar capillaries at the blood–air barrier (BAB) (Baffour et al. 2019), which is composed of alveolar type I epithelial cells and type II epithelial cells and endothelial cells. BAB disruption is an important pathological feature of ALI (Nova et al. 2019). EVs can affect the disruption of the alveolar–capillary barrier in TBI. Kerr et al. (Kerr et al. 2019) also reported that serum-derived EVs from TBI patients carry inflammasome proteins that cause lung endothelial cell pyroptosis and disrupt the integrity of the BAB, thereby exacerbating vascular permeability and pulmonary edema.

Respiratory diseases can also lead to pathophysiological alterations in the brain, which is also involved with EVs. Chavez et al. (Chavez et al. 2021) reported that circulating blood exosomes containing caspase-1 crossed the BBB and caused neuroinflammation and caspase-1/gasdermin D activation in neonatal rats with ventilation-induced lung injury (VILI); this interaction could lead to brain damage and neurodevelopmental deficits in infants who receive injurious or prolonged mechanical ventilation. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection promotes immune processes and oxidative stress, potentially triggering neurological disorders including AD and Parkinson's disease (PD) (Heneka et al. 2020). J. Ahmed et al. (Ahmed et al. 2021) demonstrated that factors transported in exosomes

from the lung to the brain influence SARS-CoV-2 infection by analyzing multiple transcriptomic datasets from SARS-CoV-2-infected lungs, RNA profiles of lung exosomes, and human-brain gene expression profiles. Also, 19 transcription factor-encoding mRNAs were overexpressed in pulmonary SARS-CoV-2 infection; among them, six transcription factors activated 469 genes associated with AD and PD, most of which are involved in inflammatory, apoptotic, and other signaling pathways that contribute to neurodegeneration (Ahmed et al. 2021). This suggests the need for further studies on the role of exosomal brain–lung communication in SARS-CoV-2 infection (Ahmed et al. 2021).

EVs in Brain–Gut Crosstalk

Communication between the gut and the brain is important for maintaining homeostasis. The gut–brain axis (GBA) is a complicated bidirectional relationship between the gut microenvironment and the brain (Raimondi et al. 2019). Disturbances in the gut microenvironment are associated with AD (Kesika et al. 2021; Megur et al. 2020), spectrum disorders (Socala et al. 2021; Srikantha & Mohajeri 2019), and PD (Mulak & Bonaz 2015; Sampson et al. 2016). The GBA contains multiple signaling pathways that transmit signals to the CNS via the vagus nerve or circulating blood. However, until recently, the significance of EVs in brain–gut communication has been gradually gaining attention (Haas-Neill & Forsythe 2020; Zhao et al. 2021).

EVs in the intestinal microenvironment can be from microorganisms and intestinal cells. Like other organisms, bacteria can also produce EVs, which are key mediators of microbial–host interactions and are widely acknowledged as an essential intercellular communication mechanism (Macia et al. 2019). The majority of EVs of gram-negative bacteria are produced by budding of the outer membrane and are termed outer membrane vesicles (OMVs); EVs formed by the outer and inner membranes of gram-negative bacteria have also been documented (Perez-Cruz et al. 2013, 2015). By incorporating cell wall modifications, gram-positive bacteria form cytoplasmic membrane vesicles that are thereafter released (Briaud and Carroll 2020; Toyofuku et al. 2019), however, the mechanism of their release is unclear (Ma and Cao 2021; Toyofuku et al. 2019). Besides bacteria, the human gut can also host a number of other microorganisms, like fungi, whose EVs can also interact with host cells and function (Rizzo et al. 2020). Bacterial EVs, like eukaryotic EVs, carry and stably store polysaccharides, proteins, DNA, RNA, metabolites, and enzymes. Their outer membranes harbor many of the same proteins as the surface of the originating bacterium (Kaparakis-Liaskos and Ferrero 2015; Liao et al. 2014). Bacterial EVs can cross the BBB and deliver cargo (Pirolli et al. 2021). Lipopolysaccharide (LPS) is present in bacterial EVs and may be linked to neuroinflammation (Pirolli et al. 2021). In addition, it is thought that OMVs can disrupt the integrity of the BBB, which may contribute to other harmful substrates and other OMVs in the BBB and thus have an impact on brain pathology (Pirolli et al. 2021). For instance, OMVs increase BBB permeability and promote astrocyte and microglia activation, and cause an inflammatory reaction and tau hyperphosphorylation by activating the glycogen synthase kinase-3 beta (GSK-3β) pathway; the end result is cognitive impairment (Wei et al. 2020). These neural effects of OMVs are similar to those seen in human AD pathology, including GSK-3β-mediated tau phosphorylation, the signature pathological marker of AD (Wei et al. 2020). The vagus nerve and blood can be used by the bacteria EVs to facilitate gut–brain communication, according to a new research by Lee et al. (Lee et al. 2020). Also, Paenalcaligenes hominis EVs increase the amount of activated microglia in the hippocampus and contribute to cognitive impairments in the brain. In animals severed by the vagus nerve, cognitive impairments were considerably decreased and hippocampus cell populations reverted to normal, suggesting that EV–vagus nerve interactions are at least partially to blame for the alterations in the brain (Lee et al. 2020). A recent report also reported that OMVs are transported from the circulatory system to brain monocyte/microglial cells and suggests that OMVs transport to the brain may be associated with infection anywhere in the body, which can lead to neuroinflammation (Ha et al. 2020).

Many neurodegenerative diseases are associated with microglia dysfunction and altered microbiome composition (Abdel-Haq et al. 2019), in this case, OMVs can deliver LPS, DNA, and RNA to the brain to activate neuroinflammation and affect gene expression in the long term. For example, *Actinomyces* OMVs cross the BBB into the brain in mice, and extracellular RNA (exRNA) transfer of OMVs to the brain causes neuroinflammatory diseases such as AD by activating the TLR8 and NF-κB inflammatory signaling pathways (Han et al. 2019). Similarly, EVs secreted by the periodontopathogen *Aggregatibacter actinomycetemcomitans* can deliver exRNAs to brain monocytes and microglia to activate IL-6 and NF-κB, thereby inducing neuroinflammation (Ha et al. 2020). *Paenalcaligenes hominis* proliferation in the gut of aged individuals accelerates LPS absorption into the blood and EV translocation to the brain, leading to cognitive impairment induced by brain inflammation (Lee et al. 2020). Bacterial EVs also carry psychoactive cargo. The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and its biosynthetic intermediates α-ketoglutarate and glutamate were present in EVs produced by *Bacillus fragilis* (Zakharzhevskaya et al. 2017). Enteric bacterial EVs contain neurotransmitters that affect the brain, and their effects on neurodegenerative diseases warrant further investigation.

In addition, EVs from gut microorganisms can also exert beneficial effects on the brain. In vitro, BDNF and proBDNF levels in HT22 hippocampus cells were increased by EVs from the gut gram-positive probiotic *Lactobacillus plantarum* (Choi et al. 2019). Intraperitoneal injection of *Lactobacillus plantarum*-derived EVs increased BDNF and neurotrophin 4/5 (Nt4/5) expression and blocked stress-induced depression-like behaviors (Choi et al. 2019). Also, EVs from the gram-positive probiotic *Bacillus subtilis* and the gram-negative probiotic *Akkermansia muciniphila* exert antidepressant effects by restoring stress-induced produced of methyl-CpG binding protein 2 (MeCP2), sirtuin 1 (Sirt1), and neurotrophic factors in the hippocampus (Choi et al. 2022).

EVs released from intestinal epithelial cells (IECs) affect the brain. The environment of EVs affects their characteristics in addition to the kind of parental cell type. IECs are exposed to food, intestinal pathogens, and microbes. The synthesis and characteristics of EVs produced from the gut can change in this environment, which may have an impact on the pathophysiology of the brain. Katakura et al. (Inotsuka et al. 2020) showed that exosomes derived from GABA-treated IECs activated SH-SY5Y cells and facilitated neurite growth. Also, exosomes found in the serum of mice orally given GABA stimulated neuronal development, suggesting that EVs released from the gut may mediate the positive effects of dietary GABA on the brain (Inotsuka et al. 2021). Intestinal microbial infections, toxins, and other factors can potentially have an impact on EVs produced from the gut (Ayyar and Moss 2021; Deng et al. 2015). Moreover, affected by this microbial–host interaction may be remote organs (Chen et al. 2019). Gut cells infected with *Escherichia coli LF*82 generate large exosomes rich in miRNAs, including miR-130a (Larabi et al. 2020). MiR-130a is associated with increased BBB permeability (Wang et al. 2016). The intestinal immune system is activated by exosomes released by IECs that contain exogenous peptides that are complexed with the major histocompatibility complex II (MHC-II) (Kojima et al. 2018). Neuroinflammation, brain damage, and alterations in neurogenesis and plasticity all cause the gut immune system to become active (Roubalova et al. 2020). In rats with sepsis-associated encephalopathy, Xi et al. (Xi et al. 2021) found that intestinal flora disturbance promoted the release of intestinal epithelium-derived exosomes, inducing hippocampal neuronal damage and apoptosis in a manner dependent on autophagy and excess circulating IL-1β; the effect was suppressed by the exosome inhibitor GW4869.

Conclusions and Future Directions

To date, studies on EV-mediated bidirectional communication between the brain and other organs are still at early stages. This is an emerging area of research and there are currently many key challenges that may hinder progress in the study of EV-mediated bidirectional communication between the brain and other organs. First, how to precisely identify organs, especially the cell types that create or receive particular EVs, so we need to find organ-specific EVs. Second, how should we find out the actual effect of the specific signals carried by EVs on the function of organs in the body? Finally, whether EVs generated in vitro could be used as next-generation therapeutic approaches, such as alternative viruses or synthetic nanovectors, for organ-targeted biotherapies. Addressing the first challenge requires to find organ-specific EVs or craft strategies to use novel technologies to label organ-specific EVs in appropriate animal models (Chand et al. 2020; Linxweiler et al. 2021). The next challenge may require the generation of genetic animal models with organ-specific defects in the production of EVs. Another thing to think about is whether EVs generated in vitro could replace viruses or synthetic nanovectors as a new vector for organ-targeted biotherapies (Zhang et al. 2022a; Fan et al. 2022; Riazifar et al. 2019; Xu et al. 2021). Also, isolation and purification of EVs is a major challenge, which requires more accurate and reliable techniques and methods to measure the number and distribution of EVs and to isolate functionally and morphologically distinct subpopulations.

This review opens up new horizons: new bidirectional communication networks between the brain and other organs are found and mapped through the use of EVs. The understanding of EVs as a transboundary signaling system provides valuable insights and may lead to more effective biological therapies. At present, more research is needed to better understand how EVs help the brain and other organs communicate with one another. With our understanding of this type of cross-border signaling expanding, there is enormous potential for answering the unanswered problems in this field.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest to report.

References

Abdel-Haq R, Schlachetzki J, Glass CK, Mazmanian SK (2019) Microbiome-microglia connections via the gut-brain axis. J Exp Med 216(1):41–59. https://doi.org/10.1084/jem.20180794

Ahmed S, Paramasivam P, Kamath M, Sharma A, Rome S, Murugesan R (2021) Genetic exchange of lung-derived exosome to brain causing neuronal changes on COVID-19 infection. Mol Neurobiol 58(10):5356–5368. https://doi.org/10.1007/s12035-021-02485-9

Atkin-Smith GK, Tixeira R, Paone S, Mathivanan S, Collins C, Liem M, Goodall KJ, Ravichandran KS, Hulett MD, Poon IK (2015) A novel mechanism of generating extracellular vesicles during apoptosis via a beads-on-a-string membrane structure. Nat Commun 6:7439. https://doi.org/10.1038/ncomms8439

Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG (2006) Neuroanatomic correlates of stroke-related myocardial injury. Neurology 66(9):1325–1329. https://doi.org/10.1212/01.wnl.0000206077.13705.6d

Ayyar KK, Moss AC (2021) Exosomes in intestinal inflammation. Front Pharmacol 12:658505. https://doi.org/10.3389/fphar.2021.658505

Baffour TP, Yasuma T, Kobayashi T, D'Alessandro-Gabazza CN, Toda M, Saiki H, Fujimoto H, Asayama K, Fujiwara K, Nishihama K, Okano T, Takeshita A, Gabazza EC (2019) Protein S is protective in acute lung injury by inhibiting cell apoptosis. Int J Mol Sci. https://doi.org/10.3390/ijms20051082

Bajaj JS, Sikaroodi M, Fagan A, Heuman D, Gilles H, Gavis EA, Fuchs M, Gonzalez-Maeso J, Nizam S, Gillevet PM, Wade JB (2019) Posttraumatic stress disorder is associated with altered gut microbiota that modulates cognitive performance in veterans with cirrhosis. Am J Physiol Gastrointest Liver Physiol 317(5):G661–G669. https://doi.org/10.1152/ajpgi.00194.2019

Bakhti M, Winter C, Simons M (2011) Inhibition of myelin membrane sheath formation by oligodendrocyte-derived exosome-like vesicles. J Biol Chem 286(1):787–796. https://doi.org/10.1074/jbc.M110.190009

Balzano T, Dadsetan S, Forteza J, Cabrera-Pastor A, Taoro-Gonzalez L, Malaguarnera M, Gil-Perotin S, Cubas-Nunez L, Casanova B, Castro-Quintas A, Ponce-Mora A, Arenas YM, Leone P, Erceg S, Llansola M, Felipo V (2020) Chronic hyperammonemia induces peripheral inflammation that leads to cognitive impairment in rats: reversed by anti-TNF-alpha treatment. J Hepatol 73(3):582–592. https://doi.org/10.1016/j.jhep.2019.01.008

Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL (2020) Transport of extracellular vesicles across the blood-brain barrier: brain pharmacokinetics and effects of inflammation. Int J Mol Sci. https://doi.org/10.3390/ijms21124407

Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL (2020) Transport of extracellular vesicles across the blood-brain barrier: brain pharmacokinetics and effects of inflammation. Int J Mol Sci. https://doi.org/10.3390/ijms21124407

Battistelli M, Falcieri E (2020) Apoptotic bodies: particular extracellular vesicles involved in intercellular communication. Biology (Basel). https://doi.org/10.3390/biology9010021

Beard K, Yang Z, Haber M, Flamholz M, Diaz-Arrastia R, Sandsmark D, Meaney DF, Issadore D (2021) Extracellular vesicles as distinct biomarker reservoirs for mild traumatic brain injury diagnosis. Brain Commun 3(3):b151. https://doi.org/10.1093/braincomms/fcab151

Braun M, Vaibhav K, Saad N, Fatima S, Brann DW, Vender JR, Wang LP, Hoda MN, Baban B, Dhandapani KM (2017) Activation of myeloid TLR4 mediates T lymphocyte polarization after traumatic brain injury. J Immunol 198(9):3615–3626. https://doi.org/10.4049/jimmunol.1601948

Braun M, Khan ZT, Khan MB, Kumar M, Ward A, Achyut BR, Arbab AS, Hess DC, Hoda MN, Baban B, Dhandapani KM, Vaibhav K (2018) Selective activation of cannabinoid receptor-2 reduces neuroinflammation after traumatic brain injury via alternative macrophage polarization. Brain Behav Immun 68:224–237. https://doi.org/10.1016/j.bbi.2017.10.021

Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF (2011) Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA 108(38):16050–16055. https://doi.org/10.1073/pnas.1102999108

Briaud P, Carroll RK (2020) Extracellular vesicle biogenesis and functions in gram-positive bacteria. Infect Immun. https://doi.org/10.1128/IAI.00433-20

Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM (2000) Central nervous system complications in liver transplant recipients–incidence, timing, and long-term follow-up. Clin Transpl 14(1):1–7. https://doi.org/10.1034/j.1399-0012.2000.140101.x

Cabrera-Pastor A, Llansola M, Montoliu C, Malaguarnera M, Balzano T, Taoro-Gonzalez L, Garcia-Garcia R, Mangas-Losada A, Izquierdo-Altarejos P, Arenas YM, Leone P, Felipo V (2019) Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic encephalopathy: underlying mechanisms and therapeutic implications. Acta Physiol (Oxf) 226(2):e13270. https://doi.org/10.1111/apha.13270

Chand S, Jo A, Vellichirammal NN, Gowen A, Guda C, Schaal V, Odegaard K, Lee H, Pendyala G, Yelamanchili SV (2020) Comprehensive characterization of nanosized extracellular vesicles from central and peripheral organs: implications for preclinical and clinical applications. ACS Appl Nano Mater 3(9):8906–8919. https://doi.org/10.1021/acsanm.0c01654

Chavez L, Meguro J, Chen S, de Paiva VN, Zambrano R, Eterno JM, Kumar R, Duncan MR, Benny M, Young KC, Dietrich WD, Brambilla R, Wu S, Schmidt AF (2021) Circulating extracellular vesicles activate the pyroptosis pathway in the brain following ventilation-induced lung injury. J Neuroinflammation 18(1):310. https://doi.org/10.1186/s12974-021-02364-z

Chen J, Huang ZP, Seok HY, Ding J, Kataoka M, Zhang Z, Hu X, Wang G, Lin Z, Wang S, Pu WT, Liao R, Wang DZ (2013) mir-17-92 cluster is required for and sufficient to induce cardiomyocyte proliferation in postnatal and adult hearts. Circ Res 112(12):1557–1566. https://doi.org/10.1161/CIRCRESAHA.112.300658

Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J (2017) Brain-heart interaction: cardiac complications after stroke. Circ Res 121(4):451–468. https://doi.org/10.1161/CIRCRESAHA.117.311170

Chen Y, Sun H, Bai Y, Zhi F (2019) Gut dysbiosis-derived exosomes trigger hepatic steatosis by transiting HMGB1 from intestinal to liver in mice. Biochem Biophys Res Commun 509(3):767–772. https://doi.org/10.1016/j.bbrc.2018.12.180

Cheng M, Liu L, Zhang T, Chen Y, Wang Q, Wu Y (2022) Extracellular vesicles derived from bone marrow mesenchymal stem cells alleviate neurological deficit and endothelial cell dysfunction after subarachnoid hemorrhage via the KLF3-AS1/miR-83–5p/TCF7L2 axis. Exp Neurol 356:114151. https://doi.org/10.1016/j.expneurol.2022.114151

Chistiakov DA, Orekhov AN, Bobryshev YV (2016) Cardiac-specific miRNA in cardiogenesis, heart function, and cardiac

pathology (with focus on myocardial infarction). J Mol Cell Cardiol 94:107–121. https://doi.org/10.1016/j.yjmcc.2016.03.015

Choi J, Kim YK, Han PL (2019) Extracellular vesicles derived from *Lactobacillus* plantarum increase BDNF expression in cultured hippocampal neurons and produce antidepressant-like effects in mice. Exp Neurobiol 28(2):158–171. https://doi.org/10.5607/en.2019.28.2.158

Choi J, Kwon H, Kim YK, Han PL (2022) Extracellular vesicles from gram-positive and gram-negative probiotics remediate stress-induced depressive behavior in mice. Mol Neurobiol 59(5):2715–2728. https://doi.org/10.1007/s12035-021-02655-9

Colombo M, Raposo G, Thery C (2014) Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol 30:255–289. https://doi.org/10.1146/annurev-cellbio-101512-122326

Comfurius P, Senden JM, Tilly RH, Schroit AJ, Bevers EM, Zwaal RF (1990) Loss of membrane phospholipid asymmetry in platelets and red cells may be associated with calcium-induced shedding of plasma membrane and inhibition of aminophospholipid translocase. Biochim Biophys Acta 1026(2):153–160. https://doi.org/10.1016/0005-2736(90)90058-v

Cui GH, Wu J, Mou FF, Xie WH, Wang FB, Wang QL, Fang J, Xu YW, Dong YR, Liu JR, Guo HD (2018) Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. FASEB J 32(2):654–668. https://doi.org/10.1096/fj.201700600R

Datta CA, Dasgheyb RM, DeVine LR, Bi H, Cole RN, Haughey NJ (2020) Stimulus-dependent modifications in astrocyte-derived extracellular vesicle cargo regulate neuronal excitability. Glia 68(1):128–144. https://doi.org/10.1002/glia.23708

de Godoy MA, Saraiva LM, de Carvalho L, Vasconcelos-Dos-Santos A, Beiral H, Ramos AB, Silva L, Leal RB, Monteiro V, Braga CV, de Araujo-Silva CA, Sinis LC, Bodart-Santos V, Kasai-Brunswick TH, Alcantara CL, Lima A, Da CSN, Galina A, Vieyra A, Ferreira ST (2018) Mesenchymal stem cells and cell-derived extracellular vesicles protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-beta oligomers. J Biol Chem 293(6):1957–1975. https://doi.org/10.1074/jbc.M117.807180

Delgado-Peraza F, Nogueras-Ortiz CJ, Volpert O, Liu D, Goetzl EJ, Mattson MP, Greig NH, Eitan E, Kapogiannis D (2021) Neuronal and astrocytic extracellular vesicle biomarkers in blood reflect brain pathology in mouse models of Alzheimer's disease. Cells. https://doi.org/10.3390/cells10050993

Dendrou CA, Fugger L, Friese MA (2015) Immunopathology of multiple sclerosis. Nat Rev Immunol 15(9):545–558. https://doi.org/10.1038/nri3871

Deng Z, Mu J, Tseng M, Wattenberg B, Zhuang X, Egilmez NK, Wang Q, Zhang L, Norris J, Guo H, Yan J, Haribabu B, Miller D, Zhang HG (2015) Enterobacteria-secreted particles induce production of exosome-like S1P-containing particles by intestinal epithelium to drive Th17-mediated tumorigenesis. Nat Commun 6:6956. https://doi.org/10.1038/ncomms7956

Deng Y, Chen D, Gao F, Lv H, Zhang G, Sun X, Liu L, Mo D, Ma N, Song L, Huo X, Yan T, Zhang J, Miao Z (2019) Exosomes derived from microRNA-138-5p-overexpressing bone marrow-derived mesenchymal stem cells confer neuroprotection to astrocytes following ischemic stroke via inhibition of LCN2. J Biol Eng 13:71. https://doi.org/10.1186/s13036-019-0193-0

Dickens AM, Tovar-Y-Romo LB, Yoo SW, Trout AL, Bae M, Kanmogne M, Megra B, Williams DW, Witwer KW, Gacias M, Tabatadze N, Cole RN, Casaccia P, Berman JW, Anthony DC, Haughey NJ (2017) Astrocyte-shed extracellular vesicles regulate the peripheral leukocyte response to inflammatory brain lesions. Sci Signal. https://doi.org/10.1126/scisignal.aai7696

Doehner W, Ural D, Haeusler KG, Celutkiene J, Bestetti R, Cavusoglu Y, Pena-Duque MA, Glavas D, Iacoviello M, Laufs U, Alvear RM, Mbakwem A, Piepoli MF, Rosen SD, Tsivgoulis G, Vitale C, Yilmaz MB, Anker SD, Filippatos G, Ruschitzka F (2018) Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy A position paper from the study group on heart and brain interaction of the heart failure association. Eur J Heart Fail 20(2):199–215. https://doi.org/10.1002/ejhf.1100

Dong C, Chen M, Cai B, Zhang C, Xiao G, Luo W (2022) Mesenchymal stem cell-derived exosomes improved cerebral infarction via transferring miR-23a-3p to activate microglia. Neuromolecular Med 24(3):290–298. https://doi.org/10.1007/s12017-021-08686-8

Duan MJ, Yan ML, Wang Q, Mao M, Su D, Sun LL, Li KX, Qu Y, Sun Q, Zhang XY, Huang SY, Ma JC, Ban T, Ai J (2018) Overexpression of miR-1 in the heart attenuates hippocampal synaptic vesicle exocytosis by the posttranscriptional regulation of SNAP-25 through the transportation of exosomes. Cell Commun Signal 16(1):91. https://doi.org/10.1186/s12964-018-0303-5

Durur DY, Tastan B, Ugur TK, Olcum M, Uzuner H, Karakulah G, Yener G, Genc S (2022) Alteration of miRNAs in small neuron-derived extracellular vesicles of Alzheimer's disease patients and the effect of extracellular vesicles on microglial immune responses. J Mol Neurosci 72(6):1182–1194. https://doi.org/10.1007/s12031-022-02012-y

Elia CA, Tamborini M, Rasile M, Desiato G, Marchetti S, Swuec P, Mazzitelli S, Clemente F, Anselmo A, Matteoli M, Malosio ML, Coco S (2019) Intracerebral injection of extracellular vesicles from mesenchymal stem cells exerts reduced Abeta plaque burden in early stages of a preclinical model of Alzheimer's disease. Cells. https://doi.org/10.3390/cells8091059

Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35(4):495–516. https://doi.org/10.1080/01926230701320337

Erwig LP, Henson PM (2008) Clearance of apoptotic cells by phagocytes. Cell Death Differ 15(2):243–250. https://doi.org/10.1038/sj.cdd.4402184

Fan Y, Chen Z, Zhang M (2022) Role of exosomes in the pathogenesis, diagnosis, and treatment of central nervous system diseases. J Transl Med 20(1):291. https://doi.org/10.1186/s12967-022-03493-6

Felipo V (2013) Hepatic encephalopathy: effects of liver failure on brain function. Nat Rev Neurosci 14(12):851–858. https://doi.org/10.1038/nrn3587

Feng N, Jia Y, Huang X (2019) Exosomes from adipose-derived stem cells alleviate neural injury caused by microglia activation via suppressing NF-kB and MAPK pathway. J Neuroimmunol 334:576996. https://doi.org/10.1016/j.jneuroim.2019.576996

Forro T, Bajko Z, Balasa A, Balasa R (2021) Dysfunction of the neurovascular unit in ischemic stroke: highlights on microRNAs and exosomes as potential biomarkers and therapy. Int J Mol Sci. https://doi.org/10.3390/ijms22115621

Friedl P, Vischer P, Freyberg MA (2002) The role of thrombospondin-1 in apoptosis. Cell Mol Life Sci 59(8):1347–1357. https://doi.org/10.1007/s00018-002-8512-9

Gabrielli M, Prada I, Joshi P, Falcicchia C, D'Arrigo G, Rutigliano G, Battocchio E, Zenatelli R, Tozzi F, Radeghieri A, Arancio O, Origlia N, Verderio C (2022) Microglial large extracellular vesicles propagate early synaptic dysfunction in Alzheimer's disease. Brain 145(8):2849–2868. https://doi.org/10.1093/brain/awac083

Geng W, Tang H, Luo S, Lv Y, Liang D, Kang X, Hong W (2019) Exosomes from miRNA-126-modified ADSCs promotes

functional recovery after stroke in rats by improving neurogenesis and suppressing microglia activation. Am J Transl Res 11(2):780–792

Go V, Sarikaya D, Zhou Y, Bowley B, Pessina MA, Rosene DL, Zhang ZG, Chopp M, Finklestein SP, Medalla M, Buller B, Moore TL (2021) Extracellular vesicles derived from bone marrow mesenchymal stem cells enhance myelin maintenance after cortical injury in aged rhesus monkeys. Exp Neurol 337:113540. https://doi.org/10.1016/j.expneurol.2020.113540

Grover SP, Mackman N (2018) Tissue factor: an essential mediator of hemostasis and trigger of thrombosis. Arterioscler Thromb Vasc Biol 38(4):709–725. https://doi.org/10.1161/ATVBAHA.117.309846

Guedes VA, Devoto C, Leete J, Sass D, Acott JD, Mithani S, Gill JM (2020) Extracellular vesicle proteins and MicroRNAs as biomarkers for traumatic brain injury. Front Neurol 11:663. https://doi.org/10.3389/fneur.2020.00663

Ha JY, Choi SY, Lee JH, Hong SH, Lee HJ (2020) Delivery of periodontopathogenic extracellular vesicles to brain monocytes and microglial IL-6 promotion by RNA cargo. Front Mol Biosci 7:596366. https://doi.org/10.3389/fmolb.2020.596366

Haas-Neill S, Forsythe P (2020) A budding relationship: bacterial extracellular vesicles in the microbiota-gut-brain axis. Int J Mol Sci. https://doi.org/10.3390/ijms21238899

Hajer GR, van Haeften TW, Visseren FL (2008) Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 29(24):2959–2971. https://doi.org/10.1093/eurheartj/ehn387

Han EC, Choi SY, Lee Y, Park JW, Hong SH, Lee HJ (2019) Extracellular RNAs in periodontopathogenic outer membrane vesicles promote TNF-alpha production in human macrophages and cross the blood-brain barrier in mice. FASEB J 33(12):13412–13422. https://doi.org/10.1096/fj.201901575R

Han M, Cao Y, Guo X, Chu X, Li T, Xue H, Xin D, Yuan L, Ke H, Li G, Wang Z (2021) Mesenchymal stem cell-derived extracellular vesicles promote microglial M2 polarization after subarachnoid hemorrhage in rats and involve the AMPK/NF-kappaB signaling pathway. Biomed Pharmacother 133:111048. https://doi.org/10.1016/j.biopha.2020.111048

Heijnen HF, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ (1999) Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood 94(11):3791–3799

Heneka MT, Golenbock D, Latz E, Morgan D, Brown R (2020) Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther 12(1):69. https://doi.org/10.1186/s13195-020-00640-3

Horn P, Erkilet G, Veulemans V, Kropil P, Schurgers L, Zeus T, Heiss C, Kelm M, Westenfeld R (2016) Microparticle-induced coagulation relates to coronary artery atherosclerosis in severe aortic valve stenosis. PLoS One 11(3):e151499. https://doi.org/10.1371/journal.pone.0151499

Huang M, Hu YY, Dong XQ (2009) High concentrations of procoagulant microparticles in the cerebrospinal fluid and peripheral blood of patients with acute basal ganglia hemorrhage are associated with poor outcome. Surg Neurol 72(5):481–489. https://doi.org/10.1016/j.surneu.2008.12.016

Huang S, Ge X, Yu J, Han Z, Yin Z, Li Y, Chen F, Wang H, Zhang J, Lei P (2018a) Increased miR-124-3p in microglial exosomes following traumatic brain injury inhibits neuronal inflammation and contributes to neurite outgrowth via their transfer into neurons. FASEB J 32(1):512–528. https://doi.org/10.1096/fj.201700673R

Huang X, Ding J, Li Y, Liu W, Ji J, Wang H, Wang X (2018b) Exosomes derived from PEDF modified adipose-derived mesenchymal stem cells ameliorate cerebral ischemia-reperfusion injury by regulation of autophagy and apoptosis. Exp Cell Res 371(1):269–277. https://doi.org/10.1016/j.yexcr.2018.08.021

Hugel B, Martinez MC, Kunzelmann C, Freyssinet JM (2005) Membrane microparticles: two sides of the coin. Physiology (bethesda) 20:22–27. https://doi.org/10.1152/physiol.00029.2004

Inotsuka R, Uchimura K, Yamatsu A, Kim M, Katakura Y (2020) gamma-aminobutyric acid (GABA) activates neuronal cells by inducing the secretion of exosomes from intestinal cells. Food Funct 11(10):9285–9290. https://doi.org/10.1039/d0fo01184c

Inotsuka R, Udono M, Yamatsu A, Kim M, Katakura Y (2021) Exosome-mediated activation of neuronal cells triggered by gamma-aminobutyric acid (GABA). Nutrients. https://doi.org/10.3390/nu13082544

Ishibe T, Nakano H, Usui T, Hiromoto N (1975) Medical treatment of male infertility. IV. Effect of pantethine on the seminal fluid in infertile patients. Nihon Funin Gakkai Zasshi 20(1):27–29

Izquierdo-Altarejos P, Martinez-Garcia M, Felipo V (2022) Extracellular vesicles from hyperammonemic rats induce neuroinflammation in cerebellum of normal rats: role of increased TNFalpha content. Front Immunol 13:921947. https://doi.org/10.3389/fimmu.2022.921947

Jiang M, Wang H, Jin M, Yang X, Ji H, Jiang Y, Zhang H, Wu F, Wu G, Lai X, Cai L, Hu R, Xu L, Li L (2018) Exosomes from MiR-30d-5p-ADSCs reverse acute ischemic stroke-induced, autophagy-mediated brain injury by promoting M2 microglial/macrophage polarization. Cell Physiol Biochem 47(2):864–878. https://doi.org/10.1159/000490078

Jiang H, Zhao H, Zhang M, He Y, Li X, Xu Y, Liu X (2022) Hypoxia induced changes of exosome cargo and subsequent biological effects. Front Immunol 13:824188. https://doi.org/10.3389/fimmu.2022.824188

Kailashiya J (2018) Platelet-derived microparticles analysis: techniques, challenges and recommendations. Anal Biochem 546:78–85. https://doi.org/10.1016/j.ab.2018.01.030

Kanekiyo T, Xu H, Bu G (2014) ApoE and Abeta in Alzheimer's disease: accidental encounters or partners? Neuron 81(4):740–754. https://doi.org/10.1016/j.neuron.2014.01.045

Kang X, Jiang L, Chen X, Wang X, Gu S, Wang J, Zhu Y, Xie X, Xiao H, Zhang J (2021) Exosomes derived from hypoxic bone marrow mesenchymal stem cells rescue OGD-induced injury in neural cells by suppressing NLRP3 inflammasome-mediated pyroptosis. Exp Cell Res 405(1):112635. https://doi.org/10.1016/j.yexcr.2021.112635

Kaparakis-Liaskos M, Ferrero RL (2015) Immune modulation by bacterial outer membrane vesicles. Nat Rev Immunol 15(6):375–387. https://doi.org/10.1038/nri3837

Karnati HK, Garcia JH, Tweedie D, Becker RE, Kapogiannis D, Greig NH (2019) Neuronal enriched extracellular vesicle proteins as biomarkers for traumatic brain injury. J Neurotrauma 36(7):975–987. https://doi.org/10.1089/neu.2018.5898

Karpman D, Stahl AL, Arvidsson I (2017) Extracellular vesicles in renal disease. Nat Rev Nephrol 13(9):545–562. https://doi.org/10.1038/nrneph.2017.98

Katsuda T, Tsuchiya R, Kosaka N, Yoshioka Y, Takagaki K, Oki K, Takeshita F, Sakai Y, Kuroda M, Ochiya T (2013) Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Sci Rep 3:1197. https://doi.org/10.1038/srep01197

Kelton JG, Warkentin TE, Hayward CP, Murphy WG, Moore JC (1992) Calpain activity in patients with thrombotic thrombocytopenic purpura is associated with platelet microparticles. Blood 80(9):2246–2251

Kerr JF, Wyllie AH, Currie AR (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26(4):239–257. https://doi.org/10.1038/bjc.1972.33

Kerr NA, de Rivero VJ, Abbassi S, Kaur H, Zambrano R, Wu S, Dietrich WD, Keane RW (2018) Traumatic brain injury-induced acute lung injury: evidence for activation and inhibition of a neural-respiratory-inflammasome axis. J Neurotrauma 35(17):2067–2076. https://doi.org/10.1089/neu.2017.5430

Kerr NA, de Rivero VJ, Umland O, Bullock MR, Conner GE, Dietrich WD, Keane RW (2019) Human lung cell pyroptosis following traumatic brain injury. Cells. https://doi.org/10.3390/cells8010069

Kesika P, Suganthy N, Sivamaruthi BS, Chaiyasut C (2021) Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. Life Sci 264:118627. https://doi.org/10.1016/j.lfs.2020.118627

Ko J, Hemphill M, Yang Z, Beard K, Sewell E, Shallcross J, Schweizer M, Sandsmark DK, Diaz-Arrastia R, Kim J, Meaney D, Issadore D (2020) Multi-dimensional mapping of brain-derived extracellular vesicle MicroRNA biomarker for traumatic brain injury diagnostics. J Neurotrauma 37(22):2424–2434. https://doi.org/10.1089/neu.2018.6220

Kojima M, Costantini TW, Eliceiri BP, Chan TW, Baird A, Coimbra R (2018) Gut epithelial cell-derived exosomes trigger posttrauma immune dysfunction. J Trauma Acute Care Surg 84(2):257–264. https://doi.org/10.1097/TA.0000000000001748

Laberge A, Arif S, Moulin VJ (2018) Microvesicles: intercellular messengers in cutaneous wound healing. J Cell Physiol 233(8):5550–5563. https://doi.org/10.1002/jcp.26426

Lackner P, Dietmann A, Beer R, Fischer M, Broessner G, Helbok R, Marxgut J, Pfausler B, Schmutzhard E (2010) Cellular microparticles as a marker for cerebral vasospasm in spontaneous subarachnoid hemorrhage. Stroke 41(10):2353–2357. https://doi.org/10.1161/STROKEAHA.110.584995

Larabi A, Dalmasso G, Delmas J, Barnich N, Nguyen H (2020) Exosomes transfer miRNAs from cell-to-cell to inhibit autophagy during infection with Crohn's disease-associated adherent-invasive *E. coli*. Gut Microbes 11(6):1677–1694. https://doi.org/10.1080/19490976.2020.1771985

Lee M, Ban JJ, Kim KY, Jeon GS, Im W, Sung JJ, Kim M (2016) Adipose-derived stem cell exosomes alleviate pathology of amyotrophic lateral sclerosis in vitro. Biochem Biophys Res Commun 479(3):434–439. https://doi.org/10.1016/j.bbrc.2016.09.069

Lee KE, Kim JK, Han SK, Lee DY, Lee HJ, Yim SV, Kim DH (2020) The extracellular vesicle of gut microbial *Paenalcaligenes hominis* is a risk factor for vagus nerve-mediated cognitive impairment. Microbiome 8(1):107. https://doi.org/10.1186/s40168-020-00881-2

Letra L, Santana I (2017) The influence of adipose tissue on brain development, cognition, and risk of neurodegenerative disorders. Adv Neurobiol 19:151–161. https://doi.org/10.1007/978-3-319-63260-5_6

Li J, Zhang D, Guo S, Zhao C, Wang L, Ma S, Guan F, Yao M (2021a) Dual-enzymatically cross-linked gelatin hydrogel promotes neural differentiation and neurotrophin secretion of bone marrow-derived mesenchymal stem cells for treatment of moderate traumatic brain injury. Int J Biol Macromol 187:200–213. https://doi.org/10.1016/j.ijbiomac.2021.07.111

Li Q, Tan Y, Chen S, Xiao X, Zhang M, Wu Q, Dong M (2021b) Irisin alleviates LPS-induced liver injury and inflammation through inhibition of NLRP3 inflammasome and NF-kappaB signaling. J Recept Signal Transduct Res 41(3):294–303. https://doi.org/10.1080/10799893.2020.1808675

Li Z, Song Y, He T, Wen R, Li Y, Chen T, Huang S, Wang Y, Tang Y, Shen F, Tian HL, Yang GY, Zhang Z (2021c) M2 microglial small extracellular vesicles reduce glial scar formation via the miR-124/STAT3 pathway after ischemic stroke in mice. Theranostics 11(3):1232–1248. https://doi.org/10.7150/thno.48761

Liao S, Klein MI, Heim KP, Fan Y, Bitoun JP, Ahn SJ, Burne RA, Koo H, Brady LJ, Wen ZT (2014) *Streptococcus mutans* extracellular DNA is upregulated during growth in biofilms, actively released via membrane vesicles, and influenced by components of the protein secretion machinery. J Bacteriol 196(13):2355–2366. https://doi.org/10.1128/JB.01493-14

Linxweiler J, Kolbinger A, Himbert D, Zeuschner P, Saar M, Stockle M, Junker K (2021) Organ-specific uptake of extracellular vesicles secreted by urological cancer cells. Cancers (Basel). https://doi.org/10.3390/cancers13194937

Liu X, Zhang M, Liu H, Zhu R, He H, Zhou Y, Zhang Y, Li C, Liang D, Zeng Q, Huang G (2021) Bone marrow mesenchymal stem cell-derived exosomes attenuate cerebral ischemia-reperfusion injury-induced neuroinflammation and pyroptosis by modulating microglia M1/M2 phenotypes. Exp Neurol 341:113700. https://doi.org/10.1016/j.expneurol.2021.113700

Liu S, Fan M, Xu JX, Yang LJ, Qi CC, Xia QR, Ge JF (2022) Exosomes derived from bone-marrow mesenchymal stem cells alleviate cognitive decline in AD-like mice by improving BDNF-related neuropathology. J Neuroinflamm 19(1):35. https://doi.org/10.1186/s12974-022-02393-2

Lloyd TE, Atkinson R, Wu MN, Zhou Y, Pennetta G, Bellen HJ (2002) Hrs regulates endosome membrane invagination and tyrosine kinase receptor signaling in Drosophila. Cell 108(2):261–269. https://doi.org/10.1016/s0092-8674(02)00611-6

Lombardi M, Parolisi R, Scaroni F, Bonfanti E, Gualerzi A, Gabrielli M, Kerlero DRN, Uccelli A, Giussani P, Viani P, Garlanda C, Abbracchio MP, Chaabane L, Buffo A, Fumagalli M, Verderio C (2019) Detrimental and protective action of microglial extracellular vesicles on myelin lesions: astrocyte involvement in remyelination failure. Acta Neuropathol 138(6):987–1012. https://doi.org/10.1007/s00401-019-02049-1

Long G, Wang F, Li H, Yin Z, Sandip C, Lou Y, Wang Y, Chen C, Wang DW (2013) Circulating miR-30a, miR-126 and let-7b as biomarker for ischemic stroke in humans. BMC Neurol 13:178. https://doi.org/10.1186/1471-2377-13-178

Lv H, Li J, Che Y (2021) miR-31 from adipose stem cell-derived extracellular vesicles promotes recovery of neurological function after ischemic stroke by inhibiting TRAF6 and IRF5. Exp Neurol 342:113611. https://doi.org/10.1016/j.expneurol.2021.113611

Ma L, Cao Z (2021) Membrane vesicles from periodontal pathogens and their potential roles in periodontal disease and systemic illnesses. J Periodontal Res 56(4):646–655. https://doi.org/10.1111/jre.12884

Ma MW, Wang J, Dhandapani KM, Brann DW (2017) NADPH oxidase 2 regulates NLRP3 inflammasome activation in the brain after traumatic brain injury. Oxid Med Cell Longev 2017:6057609. https://doi.org/10.1155/2017/6057609

Macia L, Nanan R, Hosseini-Beheshti E, Grau GE (2019) Host- and microbiota-derived extracellular vesicles, immune function, and disease development. Int J Mol Sci. https://doi.org/10.3390/ijms21010107

Maltman DJ, Hardy SA, Przyborski SA (2011) Role of mesenchymal stem cells in neurogenesis and nervous system repair. Neurochem Int 59(3):347–356. https://doi.org/10.1016/j.neuint.2011.06.008

McConnell RE, Higginbotham JN, Shifrin DJ, Tabb DL, Coffey RJ, Tyska MJ (2009) The enterocyte microvillus is a vesicle-generating organelle. J Cell Biol 185(7):1285–1298. https://doi.org/10.1083/jcb.200902147

McEwen BS (2006) Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci 8(4):367–381. https://doi.org/10.31887/DCNS.2006.8.4/bmcewen

McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87(3):873–904. https://doi.org/10.1152/physrev.00041.2006

Megur A, Baltriukiene D, Bukelskiene V, Burokas A (2020) The microbiota-gut-brain axis and Alzheimer's disease: neuroinflammation is to blame? Nutrients. https://doi.org/10.3390/nu13010037

Meloux A, Rigal E, Rochette L, Cottin Y, Bejot Y, Vergely C (2018) Ischemic stroke increases heart vulnerability to ischemia-reperfusion and alters myocardial cardioprotective pathways. Stroke 49(11):2752–2760. https://doi.org/10.1161/STROKEAHA.118.022207

Mesri M, Altieri DC (1999) Leukocyte microparticles stimulate endothelial cell cytokine release and tissue factor induction in a JNK1 signaling pathway. J Biol Chem 274(33):23111–23118. https://doi.org/10.1074/jbc.274.33.23111

Min W, Wu Y, Fang Y, Hong B, Dai D, Zhou Y, Liu J, Li Q (2022) Bone marrow mesenchymal stem cells-derived exosomal microRNA-124-3p attenuates hypoxic-ischemic brain damage through depressing tumor necrosis factor receptor associated factor 6 in newborn rats. Bioengineered 13(2):3194–3206. https://doi.org/10.1080/21655979.2021.2016094

Morel N, Morel O, Petit L, Hugel B, Cochard JF, Freyssinet JM, Sztark F, Dabadie P (2008) Generation of procoagulant microparticles in cerebrospinal fluid and peripheral blood after traumatic brain injury. J Trauma 64(3):698–704. https://doi.org/10.1097/TA.0b013e31816493ad

Mulak A, Bonaz B (2015) Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol 21(37):10609–10620. https://doi.org/10.3748/wjg.v21.i37.10609

Muralidharan-Chari V, Clancy J, Plou C, Romao M, Chavrier P, Raposo G, D'Souza-Schorey C (2009) ARF6-regulated shedding of tumor cell-derived plasma membrane microvesicles. Curr Biol 19(22):1875–1885. https://doi.org/10.1016/j.cub.2009.09.059

Nikolova V, Zaidi SY, Young AH, Cleare AJ, Stone JM (2019) Gut feeling: randomized controlled trials of probiotics for the treatment of clinical depression: Systematic review and meta-analysis. Ther Adv Psychopharmacol 9:667541765. https://doi.org/10.1177/2045125319859963

Nogueras-Ortiz CJ, Mahairaki V, Delgado-Peraza F, Das D, Avgerinos K, Eren E, Hentschel M, Goetzl EJ, Mattson MP, Kapogiannis D (2020) Astrocyte- and neuron-derived extracellular vesicles from Alzheimer's disease patients effect complement-mediated neurotoxicity. Cells. https://doi.org/10.3390/cells9071618

Nova Z, Skovierova H, Calkovska A (2019) Alveolar-capillary membrane-related pulmonary cells as a target in endotoxin-induced acute lung injury. Int J Mol Sci. https://doi.org/10.3390/ijms20040831

Oppenheimer SM (1994) Neurogenic cardiac effects of cerebrovascular disease. Curr Opin Neurol 7(1):20–24. https://doi.org/10.1097/00019052-199402000-00005

Otero-Ortega L, Laso-Garcia F, Gomez-de FM, Rodriguez-Frutos B, Pascual-Guerra J, Fuentes B, Diez-Tejedor E, Gutierrez-Fernandez M (2017) White matter repair after extracellular vesicles administration in an experimental animal model of subcortical stroke. Sci Rep 7:44433. https://doi.org/10.1038/srep44433

Otero-Ortega L, Alonso-Lopez E, Perez-Mato M, Laso-Garcia F, Gomez-de FM, Diekhorst L, Garcia-Bermejo ML, Conde-Moreno E, Fuentes B, Alonso DLM, Armada E, Buiza-Palomino L, Diez-Tejedor E, Gutierrez-Fernandez M (2020) Similarities and differences in extracellular vesicle profiles between ischaemic stroke and myocardial infarction. Biomedicines. https://doi.org/10.3390/biomedicines9010008

Pei X, Li Y, Zhu L, Zhou Z (2019) Astrocyte-derived exosomes suppress autophagy and ameliorate neuronal damage in experimental ischemic stroke. Exp Cell Res 382(2):111474. https://doi.org/10.1016/j.yexcr.2019.06.019

Pelosi P, Severgnini P, Chiaranda M (2005) An integrated approach to prevent and treat respiratory failure in brain-injured patients. Curr Opin Crit Care 11(1):37–42. https://doi.org/10.1097/00075198-200502000-00006

Perez-Cruz C, Carrion O, Delgado L, Martinez G, Lopez-Iglesias C, Mercade E (2013) New type of outer membrane vesicle produced by the Gram-negative bacterium Shewanella vesiculosa M7T: implications for DNA content. Appl Environ Microbiol 79(6):1874–1881. https://doi.org/10.1128/AEM.03657-12

Perez-Cruz C, Delgado L, Lopez-Iglesias C, Mercade E (2015) Outer-inner membrane vesicles naturally secreted by gram-negative pathogenic bacteria. PLoS One 10(1):e116896. https://doi.org/10.1371/journal.pone.0116896

Phinney DG, Pittenger MF (2017) Concise review: MSC-derived exosomes for cell-free therapy. Stem Cells 35(4):851–858. https://doi.org/10.1002/stem.2575

Piccin A, Murphy WG, Smith OP (2007) Circulating microparticles: pathophysiology and clinical implications. Blood Rev 21(3):157–171. https://doi.org/10.1016/j.blre.2006.09.001

Pirolli NH, Bentley WE, Jay SM (2021) Bacterial extracellular vesicles and the gut-microbiota brain axis: emerging roles in communication and potential as therapeutics. Adv Biol (Weinh) 5(7):e2000540. https://doi.org/10.1002/adbi.202000540

Qiang L, Hong L, Ningfu W, Huaihong C, Jing W (2013) Expression of miR-126 and miR-508-5p in endothelial progenitor cells is associated with the prognosis of chronic heart failure patients. Int J Cardiol 168(3):2082–2088. https://doi.org/10.1016/j.ijcard.2013.01.160

Rai A, Fang H, Fatmous M, Claridge B, Poh QH, Simpson RJ, Greening DW (2021) A protocol for isolation, purification, characterization, and functional dissection of exosomes. Methods Mol Biol 2261:105–149. https://doi.org/10.1007/978-1-0716-1186-9_9

Raimondi MT, Albani D, Giordano C (2019) An organ-on-a-chip engineered platform to study the microbiota-gut-brain axis in neurodegeneration. Trends Mol Med 25(9):737–740. https://doi.org/10.1016/j.molmed.2019.07.006

Riazifar M, Mohammadi MR, Pone EJ, Yeri A, Lasser C, Segaliny AI, McIntyre LL, Shelke GV, Hutchins E, Hamamoto A, Calle EN, Crescitelli R, Liao W, Pham V, Yin Y, Jayaraman J, Lakey J, Walsh CM, Van Keuren-Jensen K, Zhao W (2019) Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. ACS Nano 13(6):6670–6688. https://doi.org/10.1021/acsnano.9b01004

Rigueira J, R, A. J., Aguiar-Ricardo, I., Goncalves, I., Santos, R., Nunes-Ferreira, A., Rodrigues, T., Cunha, N., Andre, N., Pires, R., Veiga, F., Mendes, P. M., Pinto, F. J., & Brito, D. (2021) Heart and brain interactions in heart failure: cognition, depression, anxiety, and related outcomes. Rev Port Cardiol (Engl Ed) 40(8):547–555. https://doi.org/10.1016/j.repce.2020.09.008

Rizzo J, Rodrigues ML, Janbon G (2020) Extracellular vesicles in fungi: past, present, and future perspectives. Front Cell Infect Microbiol 10:346. https://doi.org/10.3389/fcimb.2020.00346

Roubalova R, Prochazkova P, Papezova H, Smitka K, Bilej M, Tlaskalova-Hogenova H (2020) Anorexia nervosa: Gut microbiota-immune-brain interactions. Clin Nutr 39(3):676–684. https://doi.org/10.1016/j.clnu.2019.03.023

Ruan L, Wang B, ZhuGe Q, Jin K (2015) Coupling of neurogenesis and angiogenesis after ischemic stroke. Brain Res 1623:166–173. https://doi.org/10.1016/j.brainres.2015.02.042

Ruan Z, Pathak D, Venkatesan KS, Yoshii-Kitahara A, Muraoka S, Bhatt N, Takamatsu-Yukawa K, Hu J, Wang Y, Hersh S, Ericsson M, Gorantla S, Gendelman HE, Kayed R, Ikezu S, Luebke JI, Ikezu T (2021) Alzheimer's disease brain-derived extracellular vesicles spread tau pathology in interneurons. Brain 144(1):288–309. https://doi.org/10.1093/brain/awaa376

Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R,

Wittung-Stafshede P, Knight R, Mazmanian SK (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 167(6):1469–1480. https://doi.org/10.1016/j.cell.2016.11.018

Savill J (1997) Recognition and phagocytosis of cells undergoing apoptosis. Br Med Bull 53(3):491–508. https://doi.org/10.1093/oxfordjournals.bmb.a011626

Schattling B, Engler JB, Volkmann C, Rothammer N, Woo MS, Petersen M, Winkler I, Kaufmann M, Rosenkranz SC, Fejtova A, Thomas U, Bose A, Bauer S, Trager S, Miller KK, Bruck W, Duncan KE, Salinas G, Soba P, Friese MA (2019) Bassoon proteinopathy drives neurodegeneration in multiple sclerosis. Nat Neurosci 22(6):887–896. https://doi.org/10.1038/s41593-019-0385-4

Scherer PE (2019) The many secret lives of adipocytes: implications for diabetes. Diabetologia 62(2):223–232. https://doi.org/10.1007/s00125-018-4777-x

Schoch B, Regel JP, Wichert M, Gasser T, Volbracht L, Stolke D (2007) Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. Neurosurgery 60(5):828–836. https://doi.org/10.1227/01.NEU.0000255440.21495.80

Sha S, Shen X, Cao Y, Qu L (2021) Mesenchymal stem cells-derived extracellular vesicles ameliorate Alzheimer's disease in rat models via the microRNA-29c-3p/BACE1 axis and the Wnt/beta-catenin pathway. Aging (Albany NY) 13(11):15285–15306. https://doi.org/10.18632/aging.203088

Shen M, Zheng R, Kan X (2022) Neuroprotection of bone marrow-derived mesenchymal stem cell-derived extracellular vesicle-enclosed miR-410 correlates with HDAC4 knockdown in hypoxic-ischemic brain damage. Neurochem Res 47(10):3150–3166. https://doi.org/10.1007/s11064-022-03670-5

Shi K, Zhang J, Dong JF, Shi FD (2019) Dissemination of brain inflammation in traumatic brain injury. Cell Mol Immunol 16(6):523–530. https://doi.org/10.1038/s41423-019-0213-5

Shi X, Zhong X, Deng L, Wu X, Zhang P, Zhang X, Wang G (2022) Mesenchymal stem cell-derived extracellular vesicle-enclosed microRNA-93 prevents hypoxic-ischemic brain damage in rats. Neuroscience 500:12–25. https://doi.org/10.1016/j.neuroscience.2022.06.037

Singleton Q, Vaibhav K, Braun M, Patel C, Khayrullin A, Mendhe B, Lee BR, Kolhe R, Kaiser H, Awad ME, Fariyike T, Elsayed R, Elsalanty M, Isales CM, Liu Y, Hamrick MW, Dhandapani KM, Fulzele S (2019) Bone marrow derived extracellular vesicles activate osteoclast differentiation in traumatic brain injury induced bone loss. Cells. https://doi.org/10.3390/cells8010063

Socala K, Doboszewska U, Szopa A, Serefko A, Wlodarczyk M, Zielinska A, Poleszak E, Fichna J, Wlaz P (2021) The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res 172:105840. https://doi.org/10.1016/j.phrs.2021.105840

Srikantha P, Mohajeri MH (2019) The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. Int J Mol Sci. https://doi.org/10.3390/ijms20092115

Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90(5):1977–1981. https://doi.org/10.1073/pnas.90.5.1977

Su H, Rustam YH, Masters CL, Makalic E, McLean CA, Hill AF, Barnham KJ, Reid GE, Vella LJ (2021) Characterization of brain-derived extracellular vesicle lipids in Alzheimer's disease. J Extracell Vesicles 10(7):e12089. https://doi.org/10.1002/jev2.12089

Sun LL, Duan MJ, Ma JC, Xu L, Mao M, Biddyut D, Wang Q, Yang C, Zhang S, Xu Y, Yang L, Tian Y, Liu Y, Xia SN, Li KX, Jin Z, Xiong Q, Ai J (2018) Myocardial infarction-induced hippocampal microtubule damage by cardiac originating microRNA-1 in mice. J Mol Cell Cardiol 120:12–27. https://doi.org/10.1016/j.yjmcc.2018.05.009

Sun X, Zheng X, Zhang X, Zhang Y, Luo G (2020) Exosomal microRNA-23b-3p from bone marrow mesenchymal stem cells maintains T helper/Treg balance by downregulating the PI3k/Akt/NF-kappaB signaling pathway in intracranial aneurysm. Brain Res Bull 165:305–315. https://doi.org/10.1016/j.brainresbull.2020.09.003

Takahashi Y, Nishikawa M, Shinotsuka H, Matsui Y, Ohara S, Imai T, Takakura Y (2013) Visualization and in vivo tracking of the exosomes of murine melanoma B16-BL6 cells in mice after intravenous injection. J Biotechnol 165(2):77–84. https://doi.org/10.1016/j.jbiotec.2013.03.013

Takizawa F, Tsuji S, Nagasawa S (1996) Enhancement of macrophage phagocytosis upon iC3b deposition on apoptotic cells. FEBS Lett 397(2–3):269–272. https://doi.org/10.1016/s0014-5793(96)01197-0

Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, Wolfrum C, Rao TN, Winnay JN, Garcia-Martin R, Grinspoon SK, Gorden P, Kahn CR (2017) Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 542(7642):450–455. https://doi.org/10.1038/nature21365

Tian C, Gao L, Rudebush TL, Yu L, Zucker IH (2022a) Extracellular vesicles regulate sympatho-excitation by Nrf2 in heart failure. Circ Res 131(8):687–700. https://doi.org/10.1161/CIRCRESAHA.122.320916

Tian J, Yao H, Liu Y, Wang X, Wu J, Wang J, Yu D, Xie Y, Gao J, Zhu Y, Yang C (2022b) Extracellular vesicles from bone marrow stromal cells reduce the impact of stroke on glial cell activation and blood brain-barrier permeability via a putative miR-124/PRX1 signalling pathway. Eur J Neurosci 56(2):3786–3805. https://doi.org/10.1111/ejn.15669

Tokgozoglu SL, Batur MK, Topcuoglu MA, Saribas O, Kes S, Oto A (1999) Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke 30(7):1307–1311. https://doi.org/10.1161/01.str.30.7.1307

Toyofuku M, Nomura N, Eberl L (2019) Types and origins of bacterial membrane vesicles. Nat Rev Microbiol 17(1):13–24. https://doi.org/10.1038/s41579-018-0112-2

Turturici G, Tinnirello R, Sconzo G, Geraci F (2014) Extracellular membrane vesicles as a mechanism of cell-to-cell communication: advantages and disadvantages. Am J Physiol Cell Physiol 306(7):C621–C633. https://doi.org/10.1152/ajpcell.00228.2013

Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9(6):654–659. https://doi.org/10.1038/ncb1596

van Niel G, D'Angelo G, Raposo G (2018) Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 19(4):213–228. https://doi.org/10.1038/nrm.2017.125

Venkat P, Chen J, Chopp M (2018) Exosome-mediated amplification of endogenous brain repair mechanisms and brain and systemic organ interaction in modulating neurological outcome after stroke. J Cereb Blood Flow Metab 38(12):2165–2178. https://doi.org/10.1177/0271678X18782789

Villarroya-Beltri C, Baixauli F, Mittelbrunn M, Fernandez-Delgado I, Torralba D, Moreno-Gonzalo O, Baldanta S, Enrich C, Guerra S, Sanchez-Madrid F (2016) ISGylation controls exosome secretion by promoting lysosomal degradation of MVB proteins. Nat Commun 7:13588. https://doi.org/10.1038/ncomms13588

Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, Richardson JA, Bassel-Duby R, Olson EN (2008) The

endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell 15(2):261–271. https://doi.org/10.1016/j.devcel.2008.07.002

Wang S, Cesca F, Loers G, Schweizer M, Buck F, Benfenati F, Schachner M, Kleene R (2011) Synapsin I is an oligomannose-carrying glycoprotein, acts as an oligomannose-binding lectin, and promotes neurite outgrowth and neuronal survival when released via glia-derived exosomes. J Neurosci 31(20):7275–7290. https://doi.org/10.1523/JNEUROSCI.6476-10.2011

Wang MD, Wang Y, Xia YP, Dai JW, Gao L, Wang SQ, Wang HJ, Mao L, Li M, Yu SM, Tu Y, He QW, Zhang GP, Wang L, Xu GZ, Xu HB, Zhu LQ, Hu B (2016) High serum MiR-130a levels are associated with severe Perihematomal Edema and predict adverse outcome in acute ICH. Mol Neurobiol 53(2):1310–1321. https://doi.org/10.1007/s12035-015-9099-0

Wang J, Ma MW, Dhandapani KM, Brann DW (2017) Regulatory role of NADPH oxidase 2 in the polarization dynamics and neurotoxicity of microglia/macrophages after traumatic brain injury. Free Radic Biol Med 113:119–131. https://doi.org/10.1016/j.freeradbiomed.2017.09.017

Wang SS, Jia J, Wang Z (2018) Mesenchymal stem cell-derived extracellular vesicles suppresses iNOS expression and ameliorates neural impairment in Alzheimer's disease mice. J Alzheimers Dis 61(3):1005–1013. https://doi.org/10.3233/JAD-170848

Wang B, Zhao M, Su Z, Jin B, Yang X, Zhang C, Guo B, Li J, Hong W, Liu J, Zhao Y, Hou Y, Lai F, Zhang W, Qin L, Zhang W, Luo J, Zheng R (2022) RIIbeta-PKA in GABAergic neurons of dorsal median hypothalamus governs white adipose browning. Adv Sci (Weinh). https://doi.org/10.1002/advs.202205173

Wang J, Li L, Zhang Z, Zhang X, Zhu Y, Zhang C, Bi Y (2022b) Extracellular vesicles mediate the communication of adipose tissue with brain and promote cognitive impairment associated with insulin resistance. Cell Metab 34(9):1264–1279. https://doi.org/10.1016/j.cmet.2022.08.004

Wei S, Peng W, Mai Y, Li K, Wei W, Hu L, Zhu S, Zhou H, Jie W, Wei Z, Kang C, Li R, Liu Z, Zhao B, Cai Z (2020) Outer membrane vesicles enhance tau phosphorylation and contribute to cognitive impairment. J Cell Physiol 235(5):4843–4855. https://doi.org/10.1002/jcp.29362

Witwer KW, Thery C (2019) Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature. J Extracell Vesicles 8(1):1648167. https://doi.org/10.1080/20013078.2019.1648167

Xi S, Wang Y, Wu C, Peng W, Zhu Y, Hu W (2021) Intestinal epithelial cell exosome launches IL-1beta-mediated neuron injury in sepsis-associated encephalopathy. Front Cell Infect Microbiol 11:783049. https://doi.org/10.3389/fcimb.2021.783049

Xin H, Katakowski M, Wang F, Qian JY, Liu XS, Ali MM, Buller B, Zhang ZG, Chopp M (2017) MicroRNA cluster miR-17-92 cluster in exosomes enhance neuroplasticity and functional recovery after stroke in rats. Stroke 48(3):747–753. https://doi.org/10.1161/STROKEAHA.116.015204

Xiong L, Sun L, Zhang Y, Peng J, Yan J, Liu X (2020) Exosomes from bone marrow mesenchymal stem cells can alleviate early brain injury after subarachnoid hemorrhage through miRNA129-5p-HMGB1 pathway. Stem Cells Dev 29(4):212–221. https://doi.org/10.1089/scd.2019.0206

Xu M, Feng T, Liu B, Qiu F, Xu Y, Zhao Y, Zheng Y (2021) Engineered exosomes: desirable target-tracking characteristics for cerebrovascular and neurodegenerative disease therapies. Theranostics 11(18):8926–8944. https://doi.org/10.7150/thno.62330

Yang H, Chen J (2022) Bone marrow mesenchymal stem cell-derived exosomes carrying long noncoding RNA ZFAS1 alleviate oxidative stress and inflammation in ischemic stroke by inhibiting microRNA-15a-5p. Metab Brain Dis 37(7):2545–2557. https://doi.org/10.1007/s11011-022-00997-4

Yang Y, Cai Y, Zhang Y, Liu J, Xu Z (2018) Exosomes secreted by adipose-derived stem cells contribute to angiogenesis of brain microvascular endothelial cells following oxygen-glucose deprivation in vitro through MicroRNA-181b/TRPM7 axis. J Mol Neurosci 65(1):74–83. https://doi.org/10.1007/s12031-018-1071-9

Yang D, Zhang W, Zhang H, Zhang F, Chen L, Ma L, Larcher LM, Chen S, Liu N, Zhao Q, Tran P, Chen C, Veedu RN, Wang T (2020) Progress, opportunity, and perspective on exosome isolation—efforts for efficient exosome-based theranostics. Theranostics 10(8):3684–3707. https://doi.org/10.7150/thno.41580

Yang H, Tu Z, Yang D, Hu M, Zhou L, Li Q, Yu B, Hou S (2022) Exosomes from hypoxic pre-treated ADSCs attenuate acute ischemic stroke-induced brain injury via delivery of circ-Rps5 and promote M2 microglia/macrophage polarization. Neurosci Lett 769:136389. https://doi.org/10.1016/j.neulet.2021.136389

Yasui H, Donahue DL, Walsh M, Castellino FJ, Ploplis VA (2016) Early coagulation events induce acute lung injury in a rat model of blunt traumatic brain injury. Am J Physiol Lung Cell Mol Physiol 311(1):L74–L86. https://doi.org/10.1152/ajplung.00429.2015

You Y, Joseph C, Wang C, Gupta V, Liu S, Yiannikas C, Chua BE, Chitranshi N, Shen T, Dheer Y, Invernizzi A, Borotkanics R, Barnett M, Graham SL, Klistorner A (2019) Demyelination precedes axonal loss in the transneuronal spread of human neurodegenerative disease. Brain 142(2):426–442. https://doi.org/10.1093/brain/awy338

Zakharzhevskaya NB, Vanyushkina AA, Altukhov IA, Shavarda AL, Butenko IO, Rakitina DV, Nikitina AS, Manolov AI, Egorova AN, Kulikov EE, Vishnyakov IE, Fisunov GY, Govorun VM (2017) Outer membrane vesicles secreted by pathogenic and nonpathogenic Bacteroides fragilis represent different metabolic activities. Sci Rep 7(1):5008. https://doi.org/10.1038/s41598-017-05264-6

Zhang J, Li S, Li L, Li M, Guo C, Yao J, Mi S (2015) Exosome and exosomal microRNA: trafficking, sorting, and function. Genom Proteom Bioinform 13(1):17–24. https://doi.org/10.1016/j.gpb.2015.02.001

Zhang L, Liu H, Jia L, Lyu J, Sun Y, Yu H, Li H, Liu W, Weng Y, Yu W (2019) Exosomes mediate hippocampal and cortical neuronal injury induced by hepatic ischemia-reperfusion injury through activating pyroptosis in rats. Oxid Med Cell Longev 2019:3753485. https://doi.org/10.1155/2019/3753485

Zhang J, Tan Y, Chang L, Hammock BD, Hashimoto K (2020) Increased expression of soluble epoxide hydrolase in the brain and liver from patients with major psychiatric disorders: a role of brain—liver axis. J Affect Disord 270:131–134. https://doi.org/10.1016/j.jad.2020.03.070

Zhang CN, Li FJ, Zhao ZL, Zhang JN (2021a) The role of extracellular vesicles in traumatic brain injury-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol 321(5):L885–L891. https://doi.org/10.1152/ajplung.00023.2021

Zhang Y, Zhang Y, Chopp M, Pang H, Zhang ZG, Mahmood A, Xiong Y (2021b) MiR-17-92 cluster-enriched exosomes derived from human bone marrow mesenchymal stromal cells improve tissue and functional recovery in rats after traumatic brain injury. J Neurotrauma 38(11):1535–1550. https://doi.org/10.1089/neu.2020.7575

Zhang J, Shi W, Qu D, Yu T, Qi C, Fu H (2022a) Extracellular vesicle therapy for traumatic central nervous system disorders. Stem Cell Res Ther 13(1):442. https://doi.org/10.1186/s13287-022-03106-5

Zhang M, Gong W, Zhang D, Ji M, Chen B, Chen B, Li X, Zhou Y, Dong C, Wen G, Zhan X, Wu X, Cui L, Feng Y, Wang S, Yuan H, Xu E, Xia M, Verkhratsky A, Li B (2022) Ageing

related thyroid deficiency increases brain-targeted transport of liver-derived ApoE4-laden exosomes leading to cognitive impairment. Cell Death Dis 13(4):406. https://doi.org/10.1038/s41419-022-04858-x

Zhao Z, Wang M, Tian Y, Hilton T, Salsbery B, Zhou EZ, Wu X, Thiagarajan P, Boilard E, Li M, Zhang J, Dong JF (2016) Cardiolipin-mediated procoagulant activity of mitochondria contributes to traumatic brain injury-associated coagulopathy in mice. Blood 127(22):2763–2772. https://doi.org/10.1182/blood-2015-12-688838

Zhao RT, Zhou J, Dong XL, Bi CW, Jiang RC, Dong JF, Tian Y, Yuan HJ, Zhang JN (2018) Circular ribonucleic acid expression alteration in exosomes from the brain extracellular space after traumatic brain injury in mice. J Neurotrauma 35(17):2056–2066. https://doi.org/10.1089/neu.2017.5502

Zhao L, Ye Y, Gu L, Jian Z, Stary CM, Xiong X (2021) Extracellular vesicle-derived miRNA as a novel regulatory system for bi-directional communication in gut-brain-microbiota axis. J Transl Med 19(1):202. https://doi.org/10.1186/s12967-021-02861-y

Zheng X, Hermann DM, Bahr M, Doeppner TR (2021) The role of small extracellular vesicles in cerebral and myocardial ischemia-Molecular signals, treatment targets, and future clinical translation. Stem Cells 39(4):403–413. https://doi.org/10.1002/stem.3329

Zhou M, Cai J, Tang Y, Zhao Q (2013) MiR-17-92 cluster is a novel regulatory gene of cardiac ischemic/reperfusion injury. Med Hypotheses 81(1):108–110. https://doi.org/10.1016/j.mehy.2013.03.043