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REVIEW ARTICLE

Extracellular Vesicles, Stem Cells and the Role of miRNAs in Neurodegeneration

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Abstract: There are different modalities of intercellular communication governed by cellular homeostasis. In this review, we will explore one of these forms of communication called extracellular vesicles (EVs). These vesicles are released by all cells in the body and are heterogeneous in nature. The primary function of EVs is to share information through their cargo consisting of proteins, lipids and nucleic acids (mRNA, miRNA, dsDNA *etc.*) with other cells, which have a direct consequence on their microenvironment. We will focus on the role of EVs of mesenchymal stem cells (MSCs) in the nervous system and how these participate in intercellular communication to maintain physiological function and provide neuroprotection. However, deregulation of this same communication system could play a role in several neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, multiple sclerosis, prion disease and Huntington's disease. The release of EVs from a cell provides crucial information to what is happening inside the cell and thus could be used in diagnostics and therapy. We will discuss and explore new avenues for the clinical applications of using engineered MSC-EVs and their potential therapeutic benefit in treating neurodegenerative diseases.

Keywords: Extracellular vesicles, neurodegeneration, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, prion disease, Huntington's disease, miRNA, stem cells.

1. INTRODUCTION

Neurodegenerative diseases (ND) result from brain atrophy, neuronal dysfunction and the accumulation of protein deposits. The ND such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and prion disease all occur in distinctive regions of the brain with different causes while several reports indicate that there are common molecular and cellular mechanisms. Great efforts have been made to develop therapies that challenge neurodegenerative diseases while improvements are still required. Our understanding of the cellular and molecular mechanisms involved in disease pathogenesis has improved. The challenges remaining in tackling ND are due to many reasons. These include the understanding of how neurons die and the lack of early diagnostic biomarkers. Several mechanisms may be driving the pathogenesis of the disease, such as cellular inflammation and the reduced accessibility of the central nervous system (CNS) due to the blood-brain-barrier (BBB).

Cell-based therapies have been developed in the last 20 years, and numerous advancements have been accomplished [1]. The use of stem cell therapy has shown promise and therapeutic value for ND. For the treatment of AD, the development of neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), and mesenchymal stem cells (MSCs) have all been considered. MSCs are favourites due to their ability to reprogram and therapeutic efficiency at the target site. Nevertheless, some reports have implied that the MSCs are rarely located at the target site but could secrete factors that add to the therapeutic value [2-4]. Many reports are emerging that show extracellular vesicles (EVs) secreted from cells to play a role in intercellular communication [5]. EVs derived from MSCs (MSC-EVs) are proposed to enhance the therapeutic effect at a similar level to the MSCs, indicating that MSC-EVs play a role in the efficacy of MSCs treatment [6, 7]. Several molecules have been found in EVs, including DNA, various RNA spe-

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cies (*e.g.*, miRNAs, mRNAs, tRNA), proteins and lipids [8]. These molecules are encapsulated in a protective environment and delivered horizontally or at a distant site to the recipient cells [9-11]. The EVs are the natural equivalent of nanoparticles which can transport various biomolecules between cells and to distant sites in the body [12]. They provide a means to cross the BBB and have the potential to treat several NDs such as AD and PD [13]. Herein, in this review, we explore the different ND, the role of miRNAs and adapting stem cell therapy in tackling these debilitating and life-threatening diseases.

2. MESENCHYMAL STEM CELLS (MSCS)

Mesenchymal stem cells (MSCs) are multipotent non-hematopoietic adult stem cells originating from different adult tissues [14]. MSCs are present in various tissues and organs, such as umbilical cord blood, placenta, amniotic fluid, peripheral blood, adipose tissue and bone marrow [15-19]. MSCs can undergo self-renewal and differentiate into many different cell types. They have been shown to differentiate into osteoblasts, muscle cells, adipocytes, chondrocytes, neurons, endothelial cells, hepatocytes, pancreatic β-cells and keratocytes [20-29]. MSCs offer immunomodulation benefits and could be an option for autoimmune diseases [30-32]. It is believed MSCs have lower immunogenicity due to the lack of expression of MHC class II and the co-stimulatory molecules, such as CD40 and CD80 [33]. Also, MSCs can inhibit T-lymphocytes activation and function, block dendritic cell maturation/differentiation and B cell proliferation [34-38]. MSCs can migrate and target specific sites. Several studies have shown MSCs ability to target the site of injury and promote repair of the damaged area [39-41]. Interestingly, this homing therapeutic effect can be applied to tumour microenvironments while the mechanism is still unclear [42, 43].

3. EXTRACELLULAR VESICLES

Extracellular vesicles (EVs) are small membrane vesicles secreted by various cell types and present in most bodily fluids. EV is a generic term for cell-borne particles surrounded by a lipid bilayer and are unable to replicate, *i.e.*, do not contain a functional nucleus [44-46]. EVs have repeatedly drawn interest from both the cell biology community, biotechnology and bioinformatics [47, 48]. There are three major groups of EVs according to their scale and biogenesis: exosomes (also known as small EVs (sEVs), microvesicles (also known as medium EVs (mEVs), and apoptotic bodies (also known as large EVs (lEVs) [46, 49]. Exosomes are nanosized vesicles that have a size of 30-100 nm, produced by inward budding of the limiting membrane of multivesicular bodies (MVBs), resulting in intraluminal vesicles (ILVs) being created [50]. From early to late maturation of the endosome, MVBs can fuse in the extracellular space with the plasma membrane releasing the enclosed ILVs (then called exosomes) [51]. Exosomes are essential regulators of intercellular communication, and in recent years, numerous studies have highlighted their significance in disease progression, production, or promotion.

Unlike exosomes, which are smaller and have a complex inward budding formation, the larger (100-1000nm) microvesicles, are secreted into the extracellular space through outward budding formation [45]. Their biogenesis occurs by blebbing immediately outwards and pinching the plasma membrane, releasing the nascent microvesicle into the extracellular space [52]. Microvesicles are membrane vesicles of the cell of origin, bearing proteins, nucleic acids and bioactive lipids [53]. When released in the extracellular space and entered into circulation, microvesicles may transfer their cargo to neighbouring or distant cells, resulting in phenotypic and functional changes important under several physiopathological conditions [54].

Apoptotic bodies are large vesicles formed by the physical process of causing a rise in hydrostatic pressure after cellular contraction. They are protrusive blisters that occur when the cellular plasma membrane is delaminated from the cortical cytoskeleton which it entirely covers [55]. Mostly, apoptotic bodies are considered to contain a significant amount of RNA, differently from other microvesicles [56]. Although microvesicles and exosomes may act as secure containers that mediate intercellular communication, apoptotic bodies appear after an apoptotic cell is disassembled into subcellular fragments [57].

EVs consist of nucleic acids such as DNA, RNA, miRNA, mRNA, short non-coding RNA, circular RNA and proteins, lipids, specifically plasma membrane, cytosol and those involved in lipid metabolism [58, 59]. Many researchers have analyzed miRNA as an effective diagnostic and prognostic marker for diseases. mRNA, DNA (containing oncogenic mutations), short non-coding RNA, and circular RNA are other nucleic acids that show biomarker potential [58, 59].

Post-transcription gene expression is modulated by miRNAs, which are 22 nucleotide transcripts, gaining particular interest among the transcripts residing in EVs. While the mechanism and regulation of trafficking miRNAs into sEVs is not clear. Nevertheless, the functional importance of EV-miRNAs, especially sEV-miRNAs, has gained support, including in the area of immunologic response and metastatic tumour cell growth [60]. In addition to the function of miRNAs, they are also loaded into EVs and secreted from cells as well as associated with transport proteins, *e.g.* Ago-2 or HDL (Fig. **1**) [61]. All neural cells originating from human microvascular endothelial cells (including the immortalised human brain) release EVs containing mRNA and miRNAs for epigenetic reprogramming of neural cells or post-transcriptional control of specific genes. When several types of miRNAs are isolated from cerebrospinal fluid, such as miR-100, miR-146, miR-505, and miR1274a, the expression profile of these miRNAs is altered in AD [62]. There is a correlation with the neuropsychological assessment and brain imaging in the presence of several types of serum-isolated exosomal miRNAs (miR-361-5p, miR-93-5p, miR-335-5p and miR-305p) [63].

The contribution of exosomes to neurodegenerative diseases, particularly in Alzheimer's and Parkinson's diseases, is the most studied of the neurological disorders. Neurodegenerative disorders are characterised by a gradual loss of neuronal function and/or structure, including neuronal death. Exosomes could play a neuro-protective or neuro-toxic role in these CNS pathological processes [64]. Vesicles can, in

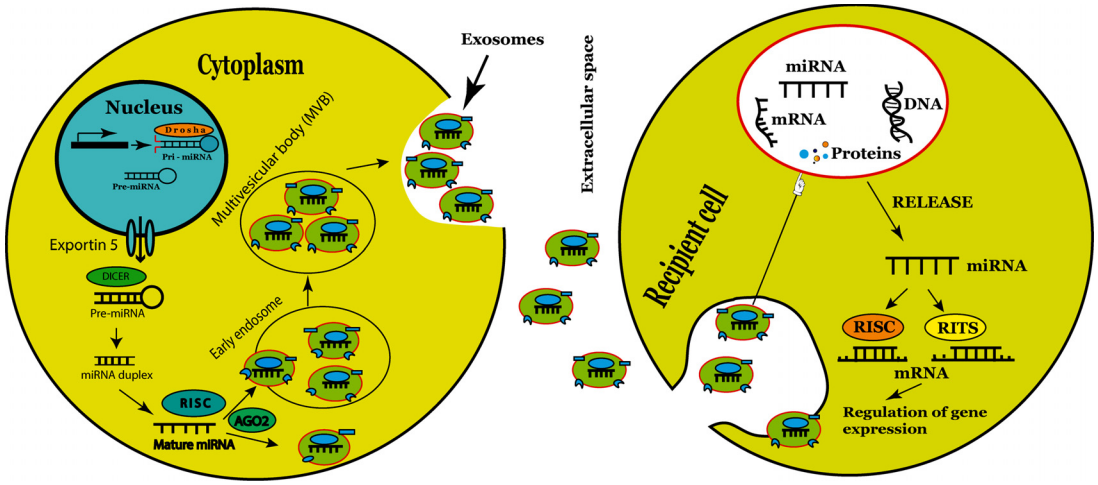

Fig. (1). Overview of miRNA synthesis and extracellular vesicle miRNA transfer to a recipient cell. miRNA genes are transcribed by RNA polymerase II (Pol II) in the nucleus of the donor cells as main miRNAs (pri-miRNAs). Microprocessor cleaved the long pri-miRNAs, which includes DROSHA, to create the miRNAs (pre-miRNAs) precursor. The pre-miRNAs are exported by exportin 5 from the nucleus into the cytoplasm and further processed by DICER, a ribonuclease III (R III) enzyme that produces RNA-induced silencing complex (RISC) to form mature miRNA. After that, the mature miRNAs can be loaded into multifunctional bodies (MVBs) produced *via* early-endosomal membrane invagination. Then, these MVBs dock on the cell membrane and release positive exosomes in serum and other biological spaces into the extracellular space. The exosomal fusion with the target cell's plasma membrane results in miRNA cargo being released into the cytosol and translational repression. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

fact, mediate the removal of toxic proteins or the transfer of exosomal neuroprotective molecules. In addition, exosomes can mediate molecular transfer as they are very likely to play a key role in intercellular interactions and tissue homeostasis maintenance. For instance, exosomes play physiological roles in neuronal growth, electrical impulse transmission, and regeneration and may therefore play a pathogenic role in neurological disease [65]. The vesicles at the axon terminal, which contain neurotransmitters or neuromodulators, release their contents by exocytosis as the nerve impulses pass along the axon in the form of the action potential [66]. On the other hand, exosomes can spread potentially toxic molecules into neural cells that are receiving them. A number of studies have focused on their role in the propagation and pathology of diseases and their utility as a diagnostic tool [64].

4. ROLE OF EXTRACELLULAR VESICLES IN THE NERVOUS SYSTEM

In the nervous system, EVs released from various glial cells (astrocytes, oligodendrocytes, and microglia) play a role in healthy conditions to maintain CNS development, such as regulating the synaptic activity and regeneration after injury. Moreover, they interact with neurons to develop and maintain the neural circuit by promoting neurite outgrowth from hippocampus neurons and increasing the survival of cortical neurons. At the same time, glial cells can promote the pathogenesis of some neurogenerative and neuroinflammatory diseases, such as Alzheimer's disease (AD), where high concentrations of microglial exosomes are found, and neural cell death that is caused by oligodendroglioma cell exosomes [65].

4.1. The Function of Astrocytes-derived EVs

Astrocytes are the most common type of glial cells within the CNS that play various roles in supporting and maintaining the homeostasis at the synapse, regulating neuronal signalling, controlling the blood flow, maintaining the blood-brain barrier (BBB), and protecting neurons against oxidative damage in the healthy nervous system [67]. In addition, astrocytes regulate the concentrations of neurotransmitter and ions, trophic factor production, maintaining the redox potential, and toxin and debris elimination from cerebrospinal fluid (CSF) [68]. While during brain injury and infection, astrocytes act as reactive immune cells mediating inflammatory responses to recruit, instruct and restrict the immune and inflammatory cells at sites of injury or disease [69]. In CNS, EVs are considered as a non-synaptic mode of communication contributing to the diffusion of signalling and brain codification [70]. Different studies have illustrated that astrocytes can secrete exosomes into the culture medium under various conditions [71-75].

Venturini and colleagues found that astrocytes-derived exosomes could target neurons in the neuron-astrocytes network and carry neuroglobin (NGB). NGB is a protein that functions as an antioxidant, anti-apoptotic, and anti-inflammatory factor, thus can act as a neuroprotectant; moreover, NGB would allow the exosomes to send messages to cells over a long distance [76]. Another study found that microvesicles released from astrocytes transfer mitochondrial DNA (mtDNA) between cells, and these microvesicles were subsequently identified as exosomes by the presence of protein markers, such as ALIX, CD9 and TSG10 [71]. The excitatory amino-acid transporters (EAAT)-1 and -2 that are responsible for transporting glutamate required for neural homeostasis have been identified to be secreted by astrocyte-derived exosomes as studied by Gosselin and colleagues [77]. Also, exosomes released from astrocytes exposed to hypoxia and ischemic conditions carry prion protein (PrP) that protects neural cells and improve neural survival under these conditions [78].

4.2. The Function of Oligodendrocytes-derived EVs

Oligodendrocytes are the myelinating cells of the CNS and arise from oligodendrocyte progenitor cells (OPC). Oligodendrocytes play a crucial role in myelin generation [79], enwrap axons to promote fast saltatory conduction of action potentials, provide metabolic support to the axon, and contribute to neuroplasticity [80]. Like astrocytes, oligodendrocytes release exosomes as a result of neurotransmitter glutamate stimulation through ionotropic glutamate receptors. In addition to RNA, the released exosomes carry various proteins, such as ALIX, TSG101, heat shock protein (HSP), tetraspanins, and myelin proteins proteolipid protein (PLP) and 2′, 3′-cyclic nucleotide 3′-phosphodiesterase (CNP) and are taken up by neurons through endocytosis [81]. Fröhlich and colleagues found various roles of oligodendrocytes-derived exosomes on neuron physiology, including an increase in the firing rate of the neuron's action potential, activating the signal transduction pathways of the cells and a change in their transcriptome. Furthermore, *in vitro* models of cerebral ischemia were used to study oligodendrocyte-derived exosomes under conditions of stroke, where they were found to possess a neuroprotective effect by transferring protective proteins (*e.g.* catalase and superoxide dismutase (SOD)) [82]. Another study illustrated that exosomes are delivered from oligodendrocytes, influencing axonal homeostasis and long-term maintenance [83].

4.3. The Function of Microglia-derived EVs

Microglia are the resident immune cells in the brain, which maintain brain homeostasis and innate immune response to CNS insult through interaction with neurons during development and adulthood [84]. Along with CNS-infiltrating macrophages, they act as a scavenger that facilitates the removal of aged, necrotic tissues and damaged neurons and synapses [85]. Also, neurotrophic factors, such as insulin-like growth factor is released by microglia to support neural survival and differentiation during postnatal development [86].

Under serotonin stimulation, microglia release exosomes, as explained by Glebov *et al.*, where they found that under physiological conditions, serotonin released from neurons could stimulate the serotonin receptors ($5\text{-}HT_{2a,b}$ and $5\text{-}HT_4$) on microglia to release exosomes [87]. Another study explained the proteomic analysis of microglia-derived exosomes isolated from the murine brain showed several enzymes, chaperones, tetraspanins and membrane receptors similar to exosomes derived from the dendritic cell and B cell. Additionally, they express aminopeptidase CD13 and monocarboxylate transporters, which are considered unique and used to distinguish them from other hematopoietic cells [88]. Also, microglia stimulated by ATP secrete EVs that have a set of proteins required for cell adhesion/organisation of extracellular matrix, degradative pathways and energy metabolism [89].

4.5. The Function of Neuronal-derived EVs

Neurons release exosomes in response to depolarization stimulation by potassium or the use of Ca^{2+} ionophores to induce excitation, as analysed from the tissue of embryonic and mature mammalian neurons [90, 91]. In addition to exosome markers, they carry subtypes of the glutamate receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), miRNAs associated with neurite (*e.g.* miR-124 and miR-1973) and also microtubule-associated protein 1B. Thus, neuron-derived exosomes play a role in exporting miRNA, modulating the excitability of neurons and neurotransmitter release [84]. Sharma and colleagues illustrated the role of neuronal exosomes in the development of a neural circuit that leads to enhanced proliferation of neural progenitor, neuronal differentiation, and circuit connectivity [92]. Another study found that neuronal exosomes regulate synaptic pruning *via* microglial phagocytosis stimulation; incubating the rat pheochromocytoma PC12 cells exosomes with microglia led to increasing complement component 3 (C3) expression level that enhanced the microglial phagocytic activity [93]. All these studies provide examples of the role of exosomes in cell-cell and glial-neuronal communications in maintaining CNS homeostasis.

5. ROLE OF EVS IN NEURODEGENERATIVE DISEASES

The contribution of EVs to neurodegenerative diseases such as Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, Huntington's, and prion diseases (Fig. **2**) has also been explored. Neurodegenerative disorders are characterised by a gradual loss of neuronal function and/or structure, including neuronal death. Exosomes could play a neuro-protective or neuro-toxic role in these CNS pathological processes [64]. Vesicles can mediate the removal of toxic proteins or the transfer of exosomal neuroprotective molecules. In addition, exosomes can mediate molecular transfer as they are very likely to play a vital role in intercellular interactions and tissue homeostasis maintenance. For instance, exosomes play physiological roles in neuronal growth, electrical impulse transmission, and regeneration and may therefore play a pathogenic role in neurological disease [65]. The vesicles at the axon terminal, which contain neurotransmitters or neuromodulators, release their contents by exocytosis as the nerve impulses pass along the axon in the form of the action potential [66]. On the other hand, exosomes can spread potentially toxic molecules into neural cells that are receiving them. A number of studies focused on their role in the propagation and pathology of diseases and their utility as a diagnostic tool [64].

5.1. Alzheimer's Disease and miRNAs

AD is the most common and major type of dementia. It is characterised by a reduction in memory cognition and executive function, which hinders daily life. According to WHO, about 50 million people are affected by dementia, and 60-70% of cases contributed to Alzheimer's disease globally, and it is predicted that this figure would double every two years. However, the primary cause is still unknown, but the widely accepted causes are β-amyloid (Aβ) peptides accumulation and intracellular neurofibrillary tangles formation that consists of hyperphosphorylated tau protein [94].

Genetically, the apolipoprotein E (APOE) ε4 allele is the most critical risk factor for late-onset AD [95]. The human gene of APOE exists as three polymorphic alleles ε2, ε3 and ε4, which have an 8.4% worldwide frequency, 77.9% and 13.7%, respectively. While, in AD patients, the occurrence of the ε4 allele is significantly elevated up to ~40% [96]. A

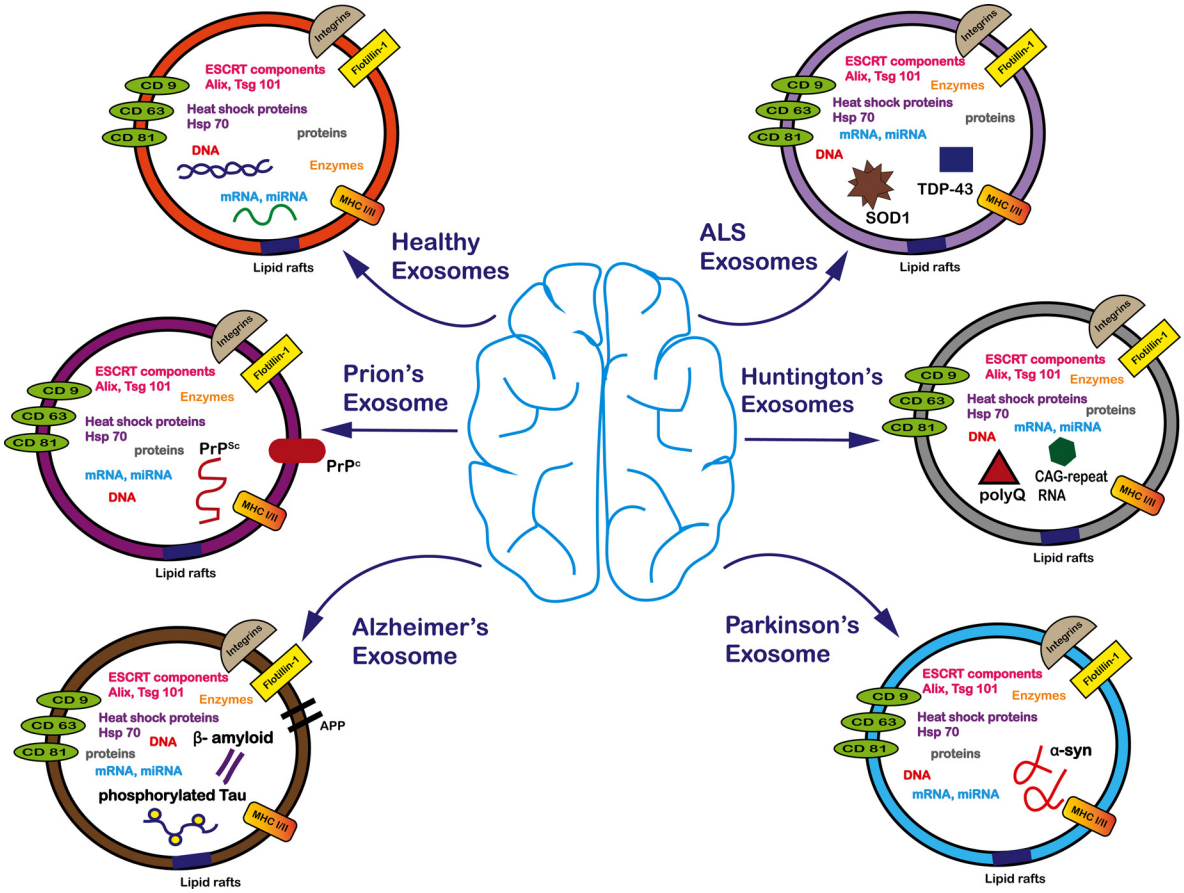

Fig. (2). EVs contents derived from normal versus ND affected brain tissue. The normal brain secretes EVs that carry cargos, including lipids, nucleic acids, and proteins, while neurodegenerative EVs carry specific proteins associated with the disease. Alzheimer's disease derived-EVs take phosphorylated tau and β-amyloid, while EVs secreted from Parkinson's disease have α-synuclein protein. Prion disease-derived EVs carry both the normal PrPc and misfolded PrPSc of the prion protein, whereas EVs secreted from Huntington and ALS diseases carry polyQ proteins and CAG-repeat RNA, SOD1 mutant form and TDP-43 protein, respectively. EVs, extracellular vesicles; PrPc, cellular prion protein; PrPSc, Scrapie prion protein; ALS, amyotrophic lateral sclerosis, SOD, superoxide dismutase. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

study in HeLa and N2a cells showed that Aβ is cleaved in early endosomes, then directed to multivesicular bodies (MVBs) and a small fraction of Aβ peptides found in the exosomes indicate a new role of exosomes in the pathogenesis of AD [97]. While another study found in addition to Aβ peptides, exosomes contain the C-terminal fragments (CTFs) of the amyloid precursor protein (APP). Also, inhibition of γ-secretase increases the cleavage by α- and β-secretase, thereby increasing the CTFs of APP in the exosomes.

Moreover, members of the secretase family that catalyse the cleavage of APP were found in the exosomes. Thus, exosomes could be used as a target for diagnosis and treatment [98]. Apoptosis could be induced by astrocytes surrounding amyloid plaques by caspase 3 activation. This has been studied by Wang's group, where they found that exosomes secreted from astrocytes induce proapoptotic effect through prostate apoptosis response 4 (PAR-4), which is a protein that induces cell sensitisation to the sphingolipid ceramide and ceramide. Antibodies against ceramide and PAR-4 halts the astrocytes apoptosis induced by amyloid *in vitro* and *in vivo* [74]. Other studies found that inhibition of the secretory pathway and exosome synthesis in microglia could alleviate tau propagation and amyloid plaque load [99, 100].

As microglia has a role in tau pathology [101], Asai and colleagues found in the mouse model that depleting microglia halts tau propagation and decreases excitability in the dentate gyrus and inhibition of the synthesis of microglia-derived exosomes both *in vitro* and *in vivo* [99]. Results from this study suggested that the propagation of tauopathy could be caused by microglia and exosomes [99]. A study by Crotti *et al.* showed that Despite Bridging Integrator 1 (BIN1), a late-onset Alzheimer's disease-associated locus overexpression could lead to the release of EVs carrying Tau protein *in vitro*. At the same time, it exacerbate *in vivo* Tau pathology in PS19 mice [102].

Strong molecular background for biomarkers of blood AD is miRNA; several miRNAs have been proposed for involvement in AD pathogenesis in experimental models of AD or clinical trials (Table **1**). Deregulated expression of miRNAs may help regulate key genes involved in AD, including amyloid development [103-106]. Specific microRNAs have also been shown to play a vital role in regulating the expression of APP and BACE1, which restricts the development of Aβ. Accumulating evidence indicates that increased APP expression can promote Aβ development, leading to neurotoxicity, synaptic failure, and ultimately

Table 1. Alzheimer's disease Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	Reference
miR- 132	↓	✓	Brain tissue	p250GAP mRNA; PTBP2	[109, 279, 280]
miR-101	↓	✓	Brain Tissue	APP, Beclin1 and Atg4d	[103, 281]
miR-106b-5p	↓	✓	Serum AD patients	APP	[282, 283]
miR-135a	↓	✓	Serum AD Patients	BACE1, APP	[284, 285]
miR-146a	↓	✓	Neocortical ECF and CSF	APP/Tau; complement factor H (CFH)	[286-288]
miR-153	↓	✓	Brain Tissue	APP	[289, 290]
miR-155	↑	✓	Neocortical ECF and CSF	APP/Tau; complement factor H (CFH)	[286, 287, 291]
miR-16	↓	✓	Brain Tissue	APP	[292]
miR-17-5p	↓	-	Brain Tissue	APP	[293]
miR-20a	↓	✓	Brain Tissue	APP	[293, 294]
miR-644	↓	✓	Cultured Neuronal Cells	APP	[294]
miR-655	↓	-	Cultured Neuronal Cells	APP	[294]
miR-9	↓ ↑	✓	AD hippocampus and medial frontal gyrus, Serum AD Patients	TGFBI, SYNJ1, SYNPR, GMEB2, p250GAP mRNA, SPT, APP	[109, 295, 296]
miR-298	↓	✓	Cultured Neuronal Cells	BACE1	[282, 297, 298]
miR-328	↓	✓	Serum AD Patients	BACE1	[282, 297, 298]
miR-423	↑	-	Hippocampus Human	IDH2	[109]
miR-98	↓	✓	Cerebellum Human	IDH2	[109]
miR-125b	↓	✓	Serum AD Patients	CDKN2, SYN-2, 15-LOX	[299]
miR-181	↓	✓	Serum AD Patients	BTBD3, TRIM, SIRT1	[295]
miR-146b	↓	✓	Hippocampus Human	TLR signaling	[299]
miR-107	↓	✓	AD Brain	BACE1	[103]
miR-124	↑	✓	AD Brain	PTPN1, BACE1	[281, 300, 301]
miR-195	↑	✓	AD Brain	ApoE/PPI Pathway	[302]
miR-29 (a/b)	↓	✓	AD Brain	BACE1, APP	[282, 303]
miR-34	↑	-	Brain Tissue	SYT1, SNAP25, STX1A, SNAP25, and UNC 13B	[304]
miR-200b	↓	✓	CSF AD Patients	BACE1, APP	[284, 305]
mir-429	↓	✓	CSF AD Patients	BACE1, APP	[284, 306]
mir-384	↓	✓	Serum AD Patients	BACE1, APP	[285]

dementia [107]. BACE1 division of APP is the first and rate-limit stage for Aβ formation, and upregulated levels of BACE1 expression and enzymatic activity in sporadic AD brains have been detected [108].

In the brain's hippocampus region, which is essential for memory and cognitive function, miR-9 is highly expressed and believed to be neuroprotective. In AD, the levels of miR-9 have been demonstrated to be reduced in primary neuronal cortical cultures, *in vivo* mouse models and in human AD brain samples [109-111]. The potential targets of miR-9 include proteins that are linked to AD pathogenesis, such as sirtuin 1 (SIRT1), BACE1, PSEN1, Nuclear Factor Kappa B

Subunit 1 (NFKB1), fibroblast growth factor receptor 1 (FGFR1), calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2), CDK6, caudal-type homeobox (CDX2) and RE1 silence transcription factor (REST) [112-115]. Tau protein can be phosphorylated by CAMKK2, which is alleviated by Ab peptide treatment of neurons. Increased activity of CAMKK2 because of Ab treatment leads to dendritic spine loss and modulation of cell signalling pathways contributing to reduced cognitive function in AD [114]. At the same time, overexpression of miR-9 provides neuroprotection due to reduced CAMKK2 activity with a direct consequence on Tau phosphorylation status and dendritic spine loss [116]. Thus, miR-9 is an interesting target for therapy in AD.

MiR-107 is another well-studied miRNA in AD. miR-107 located in the temporal cortex is down-regulated in the early stages of AD pathogenesis [117]. This miRNA targets metalloproteinase ADAM10 and BACE1, which both control the proteolytic cleavage of APP [118]. In addition, miR-107 has been demonstrated to target an actin-binding protein, cofilin, that is involved in the disassembly of actin filaments in dendrites and thus impacts cognitive function [119]. The expression of cofilin could be regulated *in vitro* with an increase of rod-like structures similar to NFT in the mouse.

Several miRNAs have been linked to AD through up-regulation or down-regulation. Most of these miRNAs are implicated in Tau phosphorylation, APP processing and neuroinflammation. Studies on microRNAs in AD have provided meaningful insights into our understanding of molecular processes by targeting different microRNAs to shed light on potential drugs. Given the lack of disease-modifying treatments, studies have consistently shown that successful management of AD can improve the quality of life for people affected and their caregivers through all stages of the disease [120, 121].

5.2. Parkinson's Disease and miRNAs

PD is the second common neurodegenerative disease caused by decreased dopamine levels in the brain due to dopaminergic cell death [122]. The incidence of PD increases with age and affects 1 to 2 people per 1000 at any time [123]. The worldwide incidence ranges from about 5 per 100,000 to over 35 per 100,000 new cases every year [124]. The most common clinical and pathological hallmark of PD is the aggregation of α-synuclein (α-syn) protein, one of the Lewy body components; it is also a presynaptic protein that binds small synaptic vesicles and has dopaminergic neurotoxicity [64]. According to a study by El-Agnaf and colleagues, α-syn was detected extracellularly in human plasma, in CSF and the culture media of α-syn transfected and untransfected human neuroblastoma cells [125]. Another study explained that α-syn is secreted by exosomes by a calcium-dependent mechanism and could propagate PD [126]. Alvarez-Erviti group showed how exosomes responsible for transporting α-syn from affected to healthy unaffected neurons *via* SH-SY5Y cells and found lysosomal dysfunction increases the exosomal transmission of α-syn to cells [127]. The type of α-syn that is present in exosomes and is considered more toxic to neighbouring cells is α-syn oligomers, as explained by the Danzer group's study. Also, they found that autophagy is the mechanism used for α-syn oligomers degradation; thus, disruption of the mechanism could increase exosome-associated α-syn oligomers [128]. A recent study found that α-syn oligomers' exosomes present in the saliva of PD patients and the ratio of α-syn oligomers to total α-syn is higher in PD than in healthy controls; thus, they suggested that salivary exosomes might be helpful as a diagnostic biomarker for PD patients than plasma [129]. Chang and colleagues studied the microglial exosomes from α-syn-induced mouse and found that the number of exosomes secreted from activated microglia was much higher than the control group; also, these exosomes showed a high expression level of MHC II and mTNF-α and could induce abnormal apoptosis of neurons [130]. Thus, these mechanisms could play a role in the pathogenesis of PD and might be a target for therapeutic approaches [130].

As mentioned by different studies that α-syn aggregates are responsible for PD progression, a study by Cooper and colleagues explained the use of α-syn siRNA to decrease the level of total and aggregated α-syn in the mouse brain *via* peripheral injection of modified exosomes [131]. While another study used catalase-loaded exosomes, where catalase is a potent antioxidant to treat PD [132].

Extracellular miRNAs are relatively stable as they are secured against degradation by binding to RNA-binding proteins and/or packaging into exosomes [133]. MiRNA dysregulation may lead to the development of different diseases, from brain disorders to cancers [134, 135]. Indeed, several studies have shown that the miRNAs expression profile is dysregulated in PD and can lead to pathogenesis of PD [136] (Table **2**). MiR-34b and miR-34c are downregulated in patients with PD and specifically in the amygdala, SNpc, frontal cortex and cerebellum, combined with a substantial decrease in PARKIN and DJ-1 protein concentrations [137]. *PRKN* and *PARK7* genes, encoding for the PARKIN and DJ-1 proteins respectively, are associated with autosomal recessive PD pathogenesis [138]. PARKIN protein is found in neuronal as well as in non-neuronal cells. *PRKN* mutations cause autosomal recessive parkinsonism in juveniles (AR-JP). The AR-JP form of PD is associated with the loss of ubiquitin-protein ligase activity, suggesting that *PRKN* mutations cause PD insurgence [139, 140].

The heat shock proteins (HSPs), known as molecular chaperones, are essential for cellular homeostasis by assisting in protein folding and degradation while inhibiting protein aggregation [141]. Perturbing HSPs in PD is believed to promote α-syn aggregation [142, 143]. The miR-16-1 has been shown to suppress HSP70 when α-syn is overexpressed in cells through negative regulation of increasing the expression of α-syn [144]. In addition, the miRNAs (miR-224, miR-320a, miR-373 and miR-379) targeting LAMP-2a are upregulated in PD, which promotes α-syn aggregation [145, 146]. Furthermore, these miRNAs lead to a decrease in LAMP-2a protein levels, promoting an increase in levels of α-syn [145]. Understanding the dynamics of miRNA control in the brain represents a crucial goal and a general topic in biomedicine, with significant implications for elucidating the pathophysiology of major neurodegenerative diseases like PD [136].

Table 2. Parkinson's Disease- Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	References
miR-106a	↑	✓	PD brain	HSC70	[145]
miR-16-1	↑	✓	Neuronal Cells	HSP70, α-SYN	[144]
miR-214	↓	✓	PD serum	α-SYN	[307-310]
miR221	↑	✓	PD- anterior cingulate gyri	SNCA, PARK2	[311]
miR-26b	↑	✓	PD brain	HSP70	[145]
miR-27	↑	✓	neuronal cells	ATP5G3	[312]
miR-29b	↑	✓	neuronal cells	HSC70	[145]
miR-301b	↑	✓	neuronal cells	HSC70	[145]
miR-34b/c	↓	✓	neuronal cells	α-SYN, PAKN, PARK7	[137, 313]
miR-7	↓	✓	neuronal cells	α-SYN, NLRP3, VDAC1, KEAP1, Bax, SIR2, RELA, GLUT3, NFκB	[313-316]
miR-153	↓	✓	neural tissue	SNCA	[309, 317]
miR-21	↑ ↓	✓	neuronal cells	LAMP2a	[145]
miR-224	↑	✓	neuronal cells	LAMP2a	[145]
miR-373	↑	-	neuronal cells	LAMP2a	[145]
miR-379	↑	✓	neuronal cells	LAMP2a	[145]
miR-128	↑	✓	brain tissue	TFEB	[318]
miR- 155	↑	✓	Neuronal Cells	ATP5G3	[312]
miR-494	↑	✓	Mice brain tissues	PARK7	[319]
miR-205	↓	✓	PD-frontal cortex	PARK8 (LRRK2)	[320]
miR-144	↑	✓	PD- anterior cingulate gyri	LRRK2, DRAM	[321]
miR-488	↑	-	PD anterior cingulate gyri	PARK2, MTFMT	[311]
miR-199b	↑	✓	PD anterior cingulate gyri	ZNF440	[311]
miR-544a	↑	✓	PD anterior cingulate gyri	XIRP2	[311]

5.3. Prion Disease and miRNAs

Prion diseases are transmissible protein mismatching disorders in which a host-encoded prion protein (PrP) is misfolded. PrP is a protein of 253 amino acids (aa) composed predominately of an alpha helix (42%) and a few beta sheets (3%) [147]. The prion protein usually contains regions called the prion domains (PrDs) necessary to form the prion state. With the exception of the Mod5p Prion domain, where these domains are intrinsically disordered and rich in glutamine and asparagines [148]. During the early 1920s, Creutzfeldt-Jakob disease (CJD) was first described [149, 150]. The predominant human prion disease subtype, sporadic Creutzfeldt-Jakob disease, occurs equally in males and females with a peak starting age from 60 to 69 years. The age of onset can vary since CJD can occur at a young age (in the 30s or 40s) and later in life [151, 152]. Many human prion diseases (75%) were classified as sporadic CJD (sCJD), which is associated with the rapid development of the disease, multifocal dementia, tiredness, insomnia, and depression [153]. Typical clinical symptoms include progressive dementia, accompanied by abnormalities in the visual and cerebellum function, myoclonia, pyramidal and extrapyramidal dysfunction or akinetic mutism [154]. Approximately 85-90 % of CJD cases occur sporadically and affect 1-1.5 persons per million per year [155]. Currently, little is known about sporadic CJD (sCJD) pathogenesis, given that there are no specific therapeutic and prophylactic interventions available for prion diseases. Therefore, active surveillance is critical in controlling and preventing human prion diseases, particularly those caused by animal-derived prion agents [147].

Current research indicates prion diseases are unique as they can result *via* three mechanisms: genetic (family), sporadic (random) and acquired (transmitted/infectious). The prion disease model is that PrP^{Sc}, the pathologic disease-causing misfolded form of the prion protein, acts as a template to transform PrP^{C} into PrP^{Sc} when it comes into contact

with a prion protein, PrP^C, resulting in two prions [156]. Prion diseases occur in humans as a sporadic, genetic, and transmissible illnesses. To date, more than 40 different PrP gene mutations have been demonstrated to segregate with the heritable human prion diseases [157, 158]. The resulting diseases have been classified according to clinical symptoms as Gerstmann – Sträussler – Scheinker syndrome (GSS), CJD, or fatal family insomnia (FFI), although all result from prion protein (PrP) encoding gene, PRNP mutations [159].

The fatal neurodegenerative disorders of human prion diseases, also named transmissible spongiform encephalopathies result from the conversion of a normal cellular prion protein (PrP^C) to an abnormally misfolded pathological (PrP^{Sc}) form [149, 150]. PrP^{Sc} accumulation leads to the onset of transmissible spongiform encephalopathies, which attack the CNS, leading to progressive neuronal degeneration and neuronal vacuolation [160].

Several miRNAs are expressed selectively in the CNS and were reported to be involved in the growth, function and pathogenesis of CNS [161]. The study of miRNAs related to prion pathogenesis has gained experimental traction as many miRNAs are altered *in vivo* and *ex vivo* models of prion diseases [162] (Table **3**). A possible association between miRNAs and prion diseases was suggested based on the colocation of PrP^C in endosomes and multivesicular bodies within RNA-induced silencing complex (RISC) components. The binding of PrP^C to the type III RNase Dicer and Argonaute (Ago) proteins, which are important components of the RNA-induced silencing complex (RISC) loading complex, was proposed as a prerequisite for the effective repression of multiple miRNA targets [163]. It has been shown in the preclinical stage of prion disease that some miRNAs are expressed in the synaptoneuromes, such as miR124a-3p, miR136-5p and miR376a-3p. In later stages of the disease, the miRNA profile changes leading to elevation in prion brains, such as miR-142-3p, miR-143-3p, miR-145a-5p, miR-146a-5p, miR-451a, miR-let-7b, miR-320, and miR-150-5p. While miR124 and miR126 are both upregulated in the brain of AD, PD and prion disease patients [109, 164-166]. During prion disease progression, many miRNAs are downregulated such as the miR-200 family members (miR-200a-3p, miR-200b-3p, and miR-200c-3p), miR-182-5p, miR-183-5p, miR-141-3p and miR-429-3p [167]. While in CJD and GSS patients, miR-146a is upregulated [168]. A difference in the miRNA profiles was observed in the CJD model of BSE-infected cynomolgus macaques [169]. In this study, miR-342-3p and miR-494 were shown to be significantly upregulated in BSE-infected macaques brains compared to healthy control. Likewise, miR-342-3p is upregulated in the brains of scrapie-infected mice and CJD patients [169, 170]. These miRNAs represent important targets in developing therapeutics.

The hallmarks of prion diseases are inflammation, and neurodegeneration and miRNAs have been identified to play a part in these processes. miR-146a has been identified as a miRNA linked to the progression of the disease by activating microglial and innate immune response [171]. In this study, miR-146a was shown to be overexpressed during prion infection and microglial cells, BV2 displayed a deregulatory response through TLR2 or TLR4 receptors. Also, miR-146 is upregulated in prion and AD patients [109, 166]. The regulation of the inflammatory pathways by miR-146a in prion disease through cell signalling involving NFkB and JAK could be an attractive therapeutic target of prion diseases.

Prion diseases are lethal mammalian neurodegenerative conditions and increasing every year with no available therapy. The biggest problem with prion diseases is that the condition is still unrecognized. Therefore, future research of prion disorders with miRNAs could provide further information for diagnostics and targeted therapy of other neurodegenerative diseases.

5.4. Huntington's Disease and miRNAs

In the 19th century, after George Huntington's lecture and explanation of the disease, it became known as Huntington's chorea. Huntington's chorea is a neurodegenerative disorder passed from generation to generation within families and is characterised by excessive choreographic gestures, behavioural and psychiatric disorders and dementia [172]. It is a disorder affecting the basal ganglia and cerebral cortex that usually develops in the middle of life but can occur as young as two or three years of age and as old as 80 years of age or older [173]. The disorder is caused by an expansion of CAG (glutamine) trinucleotide in the huntingtin (HTT) gene exon 1 located at 4p16.9, and the genetic mutation that induces the disorder is the change in the number of repetitions of three nucleic acids (C, A, and G) in the first HD gene exon's coding region [174]. The CAG trinucleotide repeat is repeated about 20 times, but an estimated doubling of the number of repetitions to 40 or more results in the disease expression [175]. HTT protein is commonly distributed in the CNS and other non-neuronal tissues. It spreads across the compartments, and in human, HTT protein is a large protein with a molecular weight of 350 kDa (3144 aa) [176]. Expansions of CAG may mediate neurodegeneration through an abnormal expansion of polyQ, and an inductive Huntington's disease (HD) transgenic mouse model was created with the first HTT exon (HTTex1), which includes the expansion of the CAG. The behavioural and pathological defects of the mouse model emerged when HTTex1 was induced and could be reversed by eliminating the inducer and the HTTex1 levels [177].

HD is characterised by widespread mis-regulation of mRNA, especially in the striatum and cortical regions [178]. This deregulation partially results from aberrant nuclear localisation of REST transcriptional repressor [179, 180]. According to recent studies, the RE1-Silencing Transcription Factor regulates the expression of large neuronal (macroRNAs) and small non-coding (miRNAs) RNAs, with specific functions in the regulation of gene expression [181, 182]. Increased REST repression contributes to improvements in the expression of different neuronal miRNAs in HD patients and HD mouse models, and HTT interacts with Argonaute proteins, which are principal members of the RNA-induced silencing complex (RISC) with the possibility that small-RNA silencing-dependent mechanisms may be involved in HD neuropathology [183]. Poly Q expansion of mutant HTT protein will inhibit the interaction between REST and HTT protein and thus promote REST aggregation in the nucleus of HD patients and inhibit the expression of related genes [115].

Table 3. Prion Disease Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	References
miR-34	↑	-	Brain	TREM2	[322, 323]
miR-342-3p	↑	✓	CJD brain	E2F1	[169, 170, 324, 325]
miR-146a	↑	✓	CJD Brain	TLR/IL1-R, CFH, IRAK-1	[168, 326]
miR-139-5p	↑	-	Microglial Cells	ROCK2	[170, 327]
miR-320	↑	✓	Mouse Brain	MAPK1/ERK2 and MAPK3/ERK1	[170, 328-330]
miR-128	↑	✓	Mouse Brain	DCX	[170, 331, 332]
miR-328	↑	✓	Mouse Brain	PLCE1	[170, 333]
miR-26a-5p	↑	✓	CJD Brain	ULK1	[162, 334, 335]
miR-16	↑	✓	Mouse brain	Neurotrophin receptor-mediated MAPK/ERK pathway	[336]
miR-93-5p	↓	✓	CJD Blood samples	IL-8, VEGF	[337-339]

Table 4. Huntington's Disease Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	References
miR-22	↓	EV	HD Brain	HDAC4, REST, Rgs2	[340, 341]
miR-132	↓	EV	HD Cortices	p250GAP, MeCP2, REST, Ago2	[279, 342]
miR-124	↓	EV	HD Brain	SOX9, PTB1, PGC1	[343, 344]
miR-196a	↑	-	HD Prefrontal Cortex	Mutant HTT, ANX1A, BDNF	[345-347]
miR-10b-5p	↑	-	HD Prefrontal Cortex/HD brain	Mutant HTT, BDNF, CREB1	[348-351]
miR-146a	↑	EV	HD Brain	HTT, TBP	[352-354]
miR-214	↑	EV	STHdhQ111/HdhQ111 cells.	HTT	[355, 356]
miR-150	↑	-	STHdhQ111/HdhQ111 cells.	HTT, Rgs8, VEGF-A	[355]
miR-125b	↑	EV	STHdhQ111/HdhQ111 cells.	HTT	[355]
miR-128	↓	EV	HD Monkey Brain	HIP-1, HTT and SP-1	[186]
miR-9	↓	EV	HD peripheral leukocytes	Foxg1	[357]

MiRNAs have recently been found to be aberrantly expressed, which plays a major role in many Poly Q diseases [184] (Table **4**). In contrast, the role of miRNAs in HD has not been well studied. Nevertheless, animal models have revealed that miRNAs can contribute to HD [185, 186]. The miR-124 expression is downregulated in HD mice models and brains of HD patients [187]. Cyclin A2 is involved in the cell cycle of dividing somatic cells has been shown to be a target of miR-124 [188]. The expression of Cyclin A2 increases when miR-124 levels decrease, which may indicate a role for miR-124 in HD [188].

Some HD cell models and animal studies have shown in recent decades that miRNAs can affect the disease at different stages, including pathogenesis, progression, and prognosis of patients through various pathways [181]. For example, in a monkey model, the miR-128 has been down-regulated in the brain of pre- and post-symptomatic HD monkeys; by suppressing HIP-1, HTT and SP-1, hence miR-128 is linked

and plays a role in HD pathogenesis [186]. As indicated above, polyQ disorders, especially HD, is a debilitating illness mentally, psychologically in the world. The genetic mutation is causing all of the HD results in an irregular expansion of a polyQ tract in the HTT protein.

5.5. Amyotrophic Lateral Sclerosis and miRNAs

Amyotrophic lateral sclerosis (ALS) is a lethal neuronal motor disease characterised by progressive spinal or bulbar-level failure of the upper and lower motor neurons with a mean death from respiratory failure of 2–3 years [189, 190]. Given the poor prognosis, the survival rate varies significantly, and up to 10 % of people with ALS have been surviving from the first symptoms for more than 8 years [191]. However, it is still unclear what causes ALS. Notable progress has been made in identifying the disease's genetic and environmental components [192].

More than 20 ALS genes have been identified, including superoxide dismutase 1 (SOD1), TAR DNA-binding protein (TARDBP), fusion protein (FUS), chromosome 9 open reading frame 72 (C9ORF72), Optineurin (OPTN), Valosin-containing protein (VCP), ubiquitin-like protein (UBQLN2), Profilin-1 (PFN1), Threonine-Protein Kinase (TBK1) and Coiled-coil-helix-coiled-coil-helix domain-containing protein 10 (CHCHD10) [193, 194]. While the pathogenesis of ALS remains largely unclear, the aetiology of the condition has shed considerable light on neuropathological characteristics and gene mutations associated with ALS. In most ALS cases, a protein named TDP-43 is the primary component of these aggregates, including cases induced by repeated expansions of C9orf72 [195, 196]. The C9orf72-related ALS repeat expansion increases with nearly 100% penetration by 80 years of age [197, 198]. No prediction of single phenotype, *i.e.* ALS, FTD or ALS / FTD, the exact age at the onset, the severity of the disease and the illness's length are theoretically unknown [199]. The repeat expansion of C9orf72 may be correlated with aberrant RNA metabolism due to the sequestration of RNA binding proteins, abnormal RNA species development or increased DNA instability [200]. Cases of ALS caused by SOD1 and FUS mutations are pathologically distinct in that they do not show TDP-43 pathology but instead irregular SOD1 and FUS protein inclusions, respectively [201].

Dysfunctional mitochondria contribute to impaired neuronal energy production and eventually results in neuronal cell death [202]. In neurodegenerative diseases, especially in ALS, aging is the key factor of mitochondrial dysfunction [203]. ALS transgenic mice (SOD1G93A) reveals their effectiveness against ALS-related neuronal cell death (anti-apoptotic) and stabilisation of mitochondria by *in vivo* investigations affecting the PI3K-AKT signalling pathway [204]. One of the crucial steps in normal brain physiology is the clearance of glutamate in the synapse. Astrocytes in the brain provide an agitating amino acid transporter of glutamate 2 [205]. Some researchers have demonstrated low levels of these transporters in ALS patients' spinal cord and cortex due to aberrant EAAT2 mRNA transcript synthesis. The altered expression of EAAT2 causes glutamate to increase, leading to death and degeneration of the motor neurons [206].

ALS contains misfolded proteins which form aggregates that, in effect, change the functioning of motor neurons. Some molecular components or proteins such as optineurin, TDP43, UBQLN2 (ubiquilin) and sarcoma fused (FUS) are associated with the aggregation of cellular proteins in ALS [207]. The metabolism of dysregulated RNA is related to protein aggregation. Various aggregation-prone RNA-binding proteins (RBPs) such as Ataxin2, TDP43, hnRNPs, FET (FUS, EWSR1, TAF15) become mislocalized and ultimately form an aggregation complex. Some miRNAs were found in ALS, which control motor neuron apoptosis, necroptosis and autophagy [208] (Table **5**). The expression of miR-34a is downregulated in an *in vitro* model of ALS and plays a major role in neurodegeneration and ALS [209]. SIRT1 is a target of miR-34a and has a protective role in disease by preventing oxidative-induced apoptosis [210]. The downregulation of miR-34a leads to increased expression of SIRT1. The upregulation of miR-34a increases p53 expression, linked to ALS, leading to the activation of many genes involved in the cell cycle [211]. In ALS patients, downregulation of miR-142-5p has been reported [212]. MiR-142-5p is an essential regulator of cell survival, and downregulation of miR-142-5p activates Nrf2 [213]. Many studies have examined miRNA in ALS patients with CSF, urine, serum or plasma. However, no biomarkers are available for this condition, possibly due to the technical variation in circulating miRNA analysis [214].

5.6. Multiple Sclerosis and miRNAs

Multiple sclerosis (MS), the most common neurological disease, is an autoimmune-mediated condition affecting the CNS and sometimes leading to significant physical or cognitive impairment and neurological disorders in young adults [215]. MS targets the myelinated axons in the CNS, killing the myelin and axons [216]. The cause is unclear, but it appears to include both genetic susceptibility and triggers, such as a virus, metabolism or environmental factors, which together contribute to a self-sustaining autoimmune condition leading to repeated immune attacks on the CNS [217]. Globally, around 2.5 million people are affected by MS, with young people between the ages of 20 and 40 most affected [218]. The higher prevalence of MS is seen in women who suffer twice as much as men [219]. MS may require a genetic predisposition. Studies indicate that the likelihood of MS in a patient's family members depends on how much genetic information they share [220]. MS is considered the most common cause of neurological impairment because MS-related inflammatory lesions can affect various systems to varying degrees and cause many neurological symptoms and comorbidities. Those include sensory impairment, visual confusion, double vision, muscle weakness, ataxia, and impaired balance, which impacts the quality of life of people affected [221, 222]. MS is challenging to handle and requires many medications working through various pathways. The diagnosis depends fundamentally on the nature and form of the disease [223].

Subtypes of MS are deemed important not just for prognosis but also for treatment decisions and include recurrence of MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive recurrence of MS

Table 5 Amyotrophic lateral sclerosis-Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	References
miR-155	↓	✓	Human ALS Cells	SOD1	[208]
miR-132-3p	↓	✓	CSF	43TARDBP, FUS and C9ORF72	[358]
miR-132-5p	↓	✓	CSF	43TARDBP, FUS and C9ORF72	[358]
let-7a-5p	↓	✓	CSF	HMGA1, MYO1F, PKM, RAB40C	[212, 359]
miR-128-3p	↓	✓	ALS Muscle Tissue	ABCG1, BAX, CTDSP1, LGALS3	[360, 361]
miR-130b-3p	↓	✓	CSF	SNAI3	[359]
miR-148a-3p	↓	✓	CSF	BAX, ITGA5	[212, 362]
miR-15a-5p	↓	✓	Peripheral Blood	HMGA1, UCP2	[363, 364]
miR-151a-5p	↓	✓	Peripheral Blood	ARHGDIA, OTUB1	[364]
miR-16-5p	↓	✓	Peripheral Blood	ARHGDIA, HDGF, HMGA1, ZYX	[212, 364]
miR-182-5p	↓	✓	Peripheral Blood	FLOT1, NFKBIB, PFN1, SMARCD3	[362, 364, 365]
miR-183-5p	↓	✓	Peripheral Blood	PTPA	[362, 364]
miR-186-5p	↓	✓	Peripheral Blood	PTTG1	[364, 366]
miR-22-3p	↓	✓	Peripheral Blood	BSG, CD151, LGALS9, PTMS	[212, 360, 364]
miR-221-3p	↓	✓	Peripheral Blood	BBC3, GRB10	[359, 362, 364, 367]
miR-223-3p	↓	✓	Peripheral Blood	HAX1, MYL9	[364, 368]
miR-23a-3p	↓	✓	Peripheral Blood	MT2A	[364, 367, 368]
miR-26a-5p	↓	✓	Peripheral Blood	HMGA1, ITGA5, PHB, PRKCD	[212, 359, 360, 364, 367]
miR-26b-5p	↓	✓	Peripheral Blood	MIEN1, MT-CO2	[364, 369]
miR-27b-3p	↓	✓	Peripheral Blood	PHB, PINK1	[212, 364, 370]
miR-30c-5p	↓	✓	Peripheral Blood	IER2, VIM	[364, 366]
miR-425-5p	↓	✓	Peripheral Blood	TACC3	[364, 371]
miR-451a	↓	✓	Peripheral Blood	CDKN2D	[359, 364, 368]
miR-550a-3p	↓	✓	Peripheral Blood	MAPK3	[361, 364]
miR-93-5p	↓	✓	Peripheral Blood	RHOC	[364, 370]

(PRMS). RRMS is the most common subtype (about 87%) with sporadic acute attacks accompanied by remission periods [224].

Inflammation of the white and grey tissue in the CNS due to focal immune cell infiltration and its cytokines is the initiating cause of MS damage. Many researchers have indicated T-helper (Th) cell involvement (also known as $CD4^+$ T cells), and adaptive immune responses that are mediated by antigen-presenting cells (APCs) association with T lymphocytes contribute to the initiation and progression of MS [225, 226]. This is evident as many studies have shown that CD8 + T cells (or cytotoxic T cells) can be present in MS lesions apart from the above-listed cells [227]. Such cells mediate the suppression and inactivation of $CD4^+$ T cells by developing cytolytic proteins such as perforin. In addition, these cells extensively increase vascular permeability, kill glial cells and cause oligodendrocyte death, playing a significant role in MS pathogenesis [226].

EVs exhibit both defensive and harmful roles in MS pathogenesis. EVs may also be considered helpful during neurological processes by restoring trophic factors, removing damaged cells, regulating synaptogenesis, and monitoring the functional status of synapses [228-230]. Recently recorded were many microvesicles produced by monocytes of MS patients compared to healthy donors [231]. Various types of RNA in several studies tend to be found in EVs or conjugates with lipoprotein as a mechanism for preventing degradation. MiRNA circulating in the blood or present in saliva, for example, is stated to be integrated into exosomes [232-236] (Table **6**). EVs play essential roles in MS growth, particularly by stimulating cells during relapses, migration through the BBB, and spreading inflammation in CNS tissue. On the other hand, a protective effect of EVs was identified with the induction of oligodendrocyte precursor cells maturing and migrating [237].

MiRNA expression has been dysregulated in various immunological diseases, such as MS and others [238]. Some researchers have shown that miRNAs can contribute to the development of MS and treatment responses [239]. Some early discoveries have found some miRNAs associated with myelination and neuroinflammatory responses [240, 241]. Most studies focus on the profiling of serum and biological fluids, which contain EVs. One such study reported several miRNAs (miR-140-5p, miR-320a, and miR-320c, miR-484, and miR-486-5p) unique to MS patients across 4 cohorts [242]. MiRNAs are also involved in adult neurogenesis that can suggest the possible role of some miRNAs in endogenous repair mechanisms in MS [243]. A Th17 cell-associated miRNA, miR-326, was described in the recent study as a major determinant of MS in a Chinese population but not of optica neuromyelitis [244]. Genetic predispositions combined with environmental factors play a significant part in the pathogenesis of multiple sclerosis. MS is a chronic disease so far without a cure, and the exact cause of MS is still unknown.

6. CURRENT DEVELOPMENTS IN STEM CELL DERIVED EV THERAPY

Stem cells have the capacity to develop into any cell/ or tissue in the human body and hence have tremendous potential for therapeutic applications in the regeneration and reconstruction of tissues [245]. It is possible to postpone the progression of incurable neurodegenerative diseases such as PD, AD, and HD thanks to stem cell therapy and, most significantly, to eliminate the source of the problem [246].

Pluripotent and multipotent stem cells have their benefits and drawbacks, respectively. Theoretically, they may be used to treat diseased or aged tissues where there are insufficient multipotent stem cells [247]. Pluripotent stem cells have not yet been used therapeutically in humans because several early animal experiments have resulted in the undesirable development of rare solid tumours, called teratomas, made up of a mixture of cell types all early germ strata. Animals were successfully treated with cells originating from pluripotent cells [248]. There has also been substantial progress in identifying the transcriptional circuitry and the epigenetic modifications associated with pluripotency [249]. This research area is moving rapidly due to tremendous advances in DNA sequencing technology, bioinformatics, and computational biology. The main pluripotency transcription factors also regulate the miRNAs involved in controlling self-renewal and differentiation of embryonic stem (ES) cells, again positively and negatively [250].

Multipotent stem cells harvested from the bone marrow were used to treat leukaemia, myeloma and lymphoma since the 1960s. Recently, some progress in using bone marrow-derived cells to treat certain diseases has been identified [251]. A team led by Professor Madrazo in 1987 recognised neural grafting as a novel approach to the replacement of damaged dopaminergic cells. Since then, neural transplantation and cell-based therapy have been considered potential therapies for PD because it is a successful candidate as a focal degeneration condition [252]. Clinical experiments of dopamine neurons derived from stem cells have undergone a new and groundbreaking age in stem cell treatment for PD. Guidelines for clinical translation to patients were then set [253, 254].

Despite the long-term emphasis on AD diagnosis, there is still no successful therapy that can interrupt or reverse the disease progression [255]. Stem cell therapy was first conducted on animal models as an approach to treat AD [256]. Neural stem cells originating from the hippocampus of neonatal rats were implanted in AD rats' brains and developed into the new cholinergic neurons enhancing spatial learning and memory capabilities of AD rodent models [257]. While stem cells hold great promise in therapeutics, scientific evidence on the safety and efficacy of their use is needed [258]. Treatment of neurodegenerative disorders involves simultaneous targeting of several impaired pathways that indicate the need for combinatorial therapy. Choosing the best therapies to combine remains a significant obstacle to be addressed [259].

Mesenchymal stem cells (MSCs) are a group of non-hematopoietic adult stem cells derived from the mesoderm, also called mesenchymal stromal cells [260]. MSCs have the capacity to differentiate into a range of cell types, including adipocytes, osteoblasts, chondrocytes, myoblasts and neuron-like cells, as typical multipotent stem cells [261]. MSCs can differentiate into neuron-like cells by modulating the plasticity of damaged host tissues, secrete growth factors that inhibit apoptosis and promote neurogenesis by neurotrophic and survival promoters [262, 263]. There is currently a great deal of interest in using MSCs in pioneering therapies to treat chronic and progressive neurodegenerative diseases that are presently incurable and whose attempts to find disease-modifying treatments, such as AD, PD, ALS and HD have failed [264]. Furthermore, MSC-induced functional recovery from stroke and brain injury is not due to MSCs that replace damaged neurons but instead to MSCs that induce growth factor production and promote intrinsic neurorestorative brain functions [265-267]. Exogenously administered MSCs can selectively target damaged tissue by a homing mechanism, interact with brain parenchymal cells, and reduce axonal inhibitory molecules' expression [268]. The MSCs can also stimulate positive growth and plasticity factors that increase neuritis outgrowth and promote neurological restoration and recovery after brain injury [268]. Administration of MSC-derived cell-free exosomes is sufficient to exert similar therapeutic effects to intact MSCs following brain injury [269]. Functional miRNAs transported between MSCs to

Table 6. Multiple Sclerosis Micro RNAs and possible targets.

miRNA	Regulation	Free miRNA or EV-associated	Region	Target	References
miR-146a	↑	✓	CSF	IRAK-1, IRAK-2, TRAF6, CFH	[371, 373]
miR-150	↑	✓	MS serum and CSF	Myb, AID, BACH1, CEBPB, CSFR	[374, 375]
miR-155	↑	✓	Serum	cMAF, FADD, IKK, JARID2, PU.1, Ripk1, SOCS1, tab2, ARK1C1, ARK1C2	[373, 376]
miR-342-3p	↓	✓	MS-Brain Tissue	AKR1C2	[376]
miR-183	↑	✓	MS-Brain Tissue	AKR1C1	[376]
miR-320a	↓	✓	MS-PBMC	MMP-9	[377]
miR-30b-5p	↓	✓	PRMS-Erythrocytes	PGC-1α	[378-380]
miR-301a	↑	✓	RRMS-PBMC	PIAS3, NKRF	[381]
miR-15a	↑	✓	MS-PBMC	BCL2	[377]
miR-16	↑	-	MS-Blood Samples	BCL2	[377, 382]
miR-23a	↓	✓	MS-Serum Samples and Brain lesions	Myocyte enhancer factor-2	[383, 384]
miR-223	↓	✓	MS-Serum Samples and Brain lesions	Myocyte enhancer factor-2	[383, 384]
miR-27	↓	✓	MS Brain Lesions	Myocyte enhancer factor-2	[384]
miR-155-3p	↑	✓	CD4+ Tcells	DnaJA2 and DnaJB1, HSP40	[385]
miR-19b	↓	✓	CD4+ Tcells	PTEN	[386]
miR-17	↓	-	CD4+ Tcells	Ikaros family zinc finger 4	[386]
miR-183C	↑	-	Th17 Cells	FOXO1	[387]
miR-96	↑	-	Th17 Cells	Il23r, Tbx21 and Ifng	[387]
miR-125a-5p	↑	✓	MS Blood Samples	DIP2A, E2F2, ADD2	[365, 388]

Table 7. Current stem cell development.

Disease	Therapy	Phase	References
Alzheimer's disease	Exosomes Derived from Allogenic Adipose Mesenchymal Stem Cells (MSCs-Exos)	I/II	[275]
Parkinson's Disease	The Effect of Adrenergic Blocker Therapy on Cardiac and Striatal Transporter Uptake in Pre-Motor and Symptomatic Parkinson's Disease	II	[389]
Huntington Disease	Cellavita HD is a stem-cell therapy	I	[390]
Prion diseases	Effectiveness of the medication quinacrine on survival in sporadic Creutzfeldt-Jakob disease (sCJD)	II	[391]
Amyotrophic Lateral Sclerosis	Intra-spinal Cord Delivery of Human Neural Stem Cells	I	[392]
Multiple Sclerosis	Neural Stem Cell Transplantation	I	[393]

neural cells *via* exosomes support the remodelling of neurites and recovery of an *in vitro* stroke rat model [270]. Provided that MSC-conditioned culture medium is rich in EVs, the most likely candidate of therapeutic effects is a complex cargo of lipids, proteins, and RNAs in EVs [271]. Exosomes derived from MSC may transfer proteins and RNAs to recipient cells and may have several effects on the growth of different tumour cells [272] (Table **7**). MSCs generate exosomes that can perform as paracrine mediators by transferring signalling molecules that regulate tumour cell prolifera-

tion, angiogenesis, and metastasis *via* several regulated cellular pathways [11, 273]. In addition, some studies show that MSC-derived exosomes provided dual miRNA mimics (miR-124 and miR-145) and decreased glioma cell migration and cancer cell stem cell properties [274].

Untreatable neurodegenerative diseases currently have the potential to become treatable with stem cell-EV therapy. The data emerging from *in vitro* and *in vivo* studies are promising, while now few clinical studies are investigating the role of MSC-EVs for the treatment of neurodegenerative diseases. A clinical trial using MSC-EVs is currently underway (Table **7**). This trial is investigating the safety and efficacy of MSC-EVs in patients with mild to moderate dementia due to AD [275]. Patients were given allogenic MSC-EVs transfected with miR-124 using stereotactic delivery [275]. The results of this trial are currently not available. Since clinical trials using MSC-EVs to treat neurodegenerative diseases have not been fully explored, some promising results are emerging from trials into other diseases [276-278]. There are many challenges still faced for the use of MSC-EVs for the treatment of neurodegenerative diseases. Neurodegenerative diseases have devastating sequelae with conventional pharmacological therapies, and to date, stem cell therapy is probably the only possible treatment method that may provide a 'cure' for neurodegenerative diseases.

CONCLUSION

In summary, the intercellular communication of MSCs EVs carries a specific cargo of miRNAs secreted into the nervous system. Their role is to maintain physiological function and provide neuroprotection. In addition, MSCs EVs help promote tissue repair and regeneration. In contrast, deregulation of this intercellular communication may promote several neurodegenerative diseases such as AD, PD, ALS, MS, prion disease and HD. Herein, we have reviewed EV miRNA profiling studies to date and their role in neurodegeneration. This information is necessary to understand as it may provide clues on how these diseases progress while providing a potential early diagnostic strategy. A few clinical trial studies are detailing the therapeutic effects of miRNA in the treatment of neurodegeneration. Therefore, studies investigating the miRNA profiling of EVs will allow the development of novel diagnostic strategies available to the clinic and provide alternative therapeutic routes for treating neurodegeneration.

LIST OF ABBREVIATIONS

AD = Alzheimer’s Disease
ALS = Amyotrophic Lateral Sclerosis
AON = Antisense Oligonucleotides
APOE = Apolipoprotein E
AR = Androgen Receptor
BBB = Blood Brain Barrier
CJD = Creutzfeldt-Jakob Disease
CNS = Central Nervous System
CSF = Cerebrospinal Fluid
DRPLA = Dentatorubral-pallidoluysian Atrophy
EGCG = Epigallocatechin Gallate
ESCs = Embryonic Stem Cells
EV = Extracellular Vesicle
FRDA = Friedreich's Ataxia
HD = Huntington’s Disease
HDL = High-density Lipoproteins
HSPs = Heat Shock Proteins
HTT = The Huntingtin (HTT)
iPSCs = Induced Pluripotent Stem Cells
lEV = Large Extracellular Vesicle
ILV = Intraluminal Vesicle
MBNL1 = Muscleblind Like Splicing Regulator 1
mEV = Medium Extracellular Vesicle
MHC = Major Histocompatibility Complex
miRNA = Micro RNA
MN = Motor Neuron
MS = Multiple Sclerosis
MSCs = Mesenchymal Stem Cells
MVB = Multivesicular Body
ND = Neurodegenerative Disease
NSCs = Neural Stem Cells
PD = Parkinson’s Disease
PRNP = Prion Protein
SBMA = Spinal-bulbar Muscular Atrophy
SCA = Spinocerebellar Ataxia
sEV = Small Extracellular Vesicle
SOD = Superoxide Dismutase
TDP-43 = TAR DNA-binding Protein 43
TNR = Trinucleotide Repeats
TREDs = Trinucleotide Repeat Expansion Disorders

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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