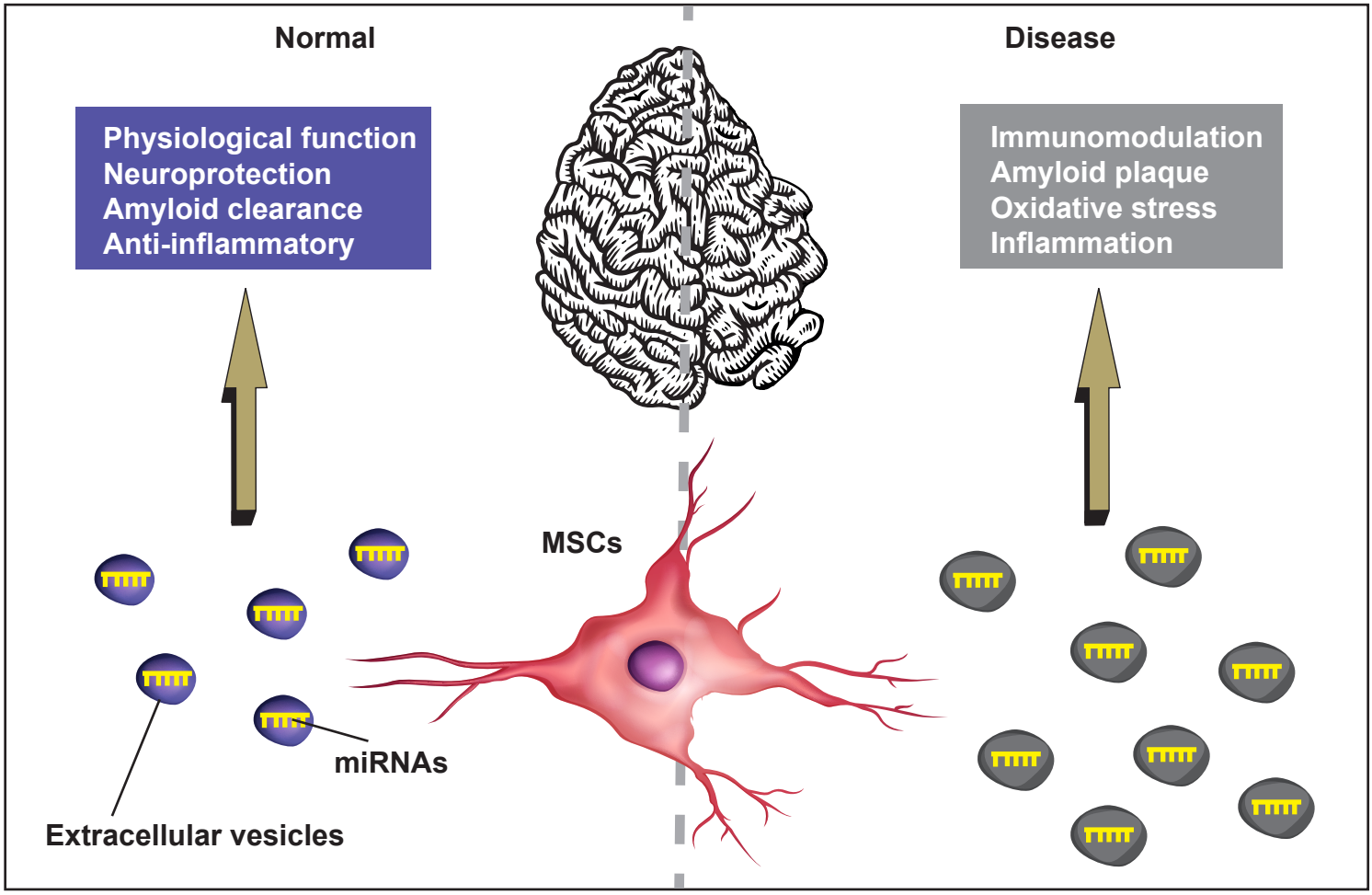
Extracellular vesicles, stem cells and the role of miRNAs in neurodegeneration.

Belkozhayev, Ayaz M., Al-Yozbaki, M., George, A., Ye Niyazova, Raigul, Sharipov, Kamalidin O., Byrne, Lee J. and Wilson, Cornelia M.

Belkozhayev AM, Al-Yozbaki M, George A, Ye Niyazova R, Sharipov KO, Byrne LJ, Wilson CM. Extracellular vesicles, stem cells and the role of miRNAs in neurodegeneration. Curr Neuropharmacol. 2021 Aug 17. doi: 10.2174/1570159X19666210817150141. Epub ahead of print. PMID: 34414870.



The role of MSC-derived extracellular vesicles and miRNAs in neurodegeneration.

Extracellular vesicles, stem cell therapy and the role of miRNAs in neurodegeneration.

Ayaz M. Belkozhayev[a,b], Minnatallah Al-Yozbaki[c], Alex George[c,d], Raigul Ye Niyazova[a], Kamalidin O. Sharipov[b], Lee J. Byrne[c] and Cornelia M. Wilson[c,e,f]

[a]al-Farabi Kazakh National University, Faculty of Biology and Biotechnology, Almaty, Republic of Kazakhstan

[b]Structural and functional genomics laboratory of M.A. Aitkhozhin Institute of Molecular Biology and Biochemistry, Almaty, Republic of Kazakhstan

[c]Canterbury Christ Church University, School of Human and Life Sciences, Life Sciences Industry Liaison Lab, Sandwich, UK

[d]Jubilee Centre for Medical Research, Jubilee Mission Medical College & Research Institute, Thrissur, Kerala, India.

[e]University of Liverpool, Institute of Translation Medicine, Dept of Molecular & Clinical

Cancer Medicine

[f]Novel Global Community Educational Foundation, Australia.

Word count:- 6,223 words

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

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 heterogenous in nature. The main function of EVs is to share information through its cargo consisting of proteins, lipids and nucleic acids (mRNA, miRNA, dsDNA etc.) with other cells which has 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 the physiological function and to provide neuroprotection. However, deregulation of this same communication system could play in role in a number of 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 provide crucial information to what is happening inside the cell and thus could be used in diagnostics as well as in therapy. In addition, we consider the role of trinucleotide repeats in neurodegenerative diseases with a view to focus on miRNA profiling, prediction of their binding and their potential role in diagnosis and stem cell therapy. We will discuss and explore new avenues for the clinical applications of using engineered MSC-EVs and their potential therapeutic benefit in the treatment of neurodegenerative diseases.

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; embryonic stem cells (ESCs); EV, extracellular vesicle; FRDA, Friedreich's ataxia; HD, Huntington's disease; HDL, High-density lipoproteins; HSPs, heat shock proteins; HTT, the huntingtin (HTT); induced pluripotent stem cells (iPSCs); 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; neural stem cells (NSCs); 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.

Introduction

Neurodegenerative diseases (ND) result from a deterioration in brain atrophy, neuronal function 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 a number of reports indicate that there are common molecular and cellular mechanisms. A great effort has been made to develop therapies to target neurodegenerative disease were improvements are still required. Our understanding of the cellular and molecular mechanism involved in the disease pathogenesis has improved. The challenges remaining in tackling ND are due to many reasons. These include the understanding of how neurons die, the lack of early diagnostic biomarkers, several mechanisms maybe 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).

In the last 20 years, cell-based therapies have been developed and numerous advancements has 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]. A number of reports are emerging that show extracellular vesicles (EVs), secreted from cells to play a role in intercellular communication [5]. MSCs derived from EVs (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]. A number of molecules have been found in EVs including DNA, various RNA species (e.g., miRNAs, mRNAs, tRNA), proteins and lipids [8]. These molecules are encapsulated in a protective environment and can be delivered horizontally or at a distant site to the recipient cells [9-11]. The EVs are natures equivalent of nanoparticles which have the ability to 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 a number of 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.

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent non-hematopoietic adult stem cells originating from different adult tissues [14]. MSCs can be found in different tissues and organs, such as umbilical cord blood, placenta, amniotic fluid, peripheral blood, adipose tissue and bone marrow [15-19]. MSCs have the ability to 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 a 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 have the ability to be migrate and target specific sites. A number of studies have shown MSCs ability to target to a 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].

What are extracellular vesicles.

Extracellular vesicles (EVs) are small membrane vesicles that are secreted by various cell-types and are present in most bodily fluids. EV is a generic term for cell-borne particles which are delimited by a lipid bilayer and cannot replicate, i.e. do not contain a functional nucleus [44]. EVs have repeatedly drawn interest from both the cell biology community, biotechnology and bioinformatics [45, 46]. 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) [44, 47].

Exosomes are nanosized vesicles which 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 [48]. 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) [49]. Exosomes are important regulators of intercellular communication, and in recent years, numerous studies have highlighted their significance in disease progression, production or promotion. There are cell-derived membrane vesicles present in virtually all

biological fluids, such as urine, blood, and cerebrospinal fluid, and are isolated primarily from cell culture medium [50, 51].

Unlike exosomes, which are smaller and have a complex inward budding formation, the larger (100-1000nm) microvesicles, are released into the extracellular space by outward budding formation [51]. 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]. Microvesicles, when released in the extracellular space and entered into circulation, may transfer their cargo to neighbouring or distant cells, resulting in phenotypic and functional changes that are important under several physio-pathological 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 which 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. Many researchers have analyzed that 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 known as showing biomarker potential [58, 59].

Post-transcription gene expression is modulated by miRNAs ~ which are 22 nucleotide transcripts this has gained special interest among the transcripts residing in EV. The molecular mechanisms and regulation of sorting miRNAs into sEVs remain poorly understood. Nevertheless, it is, thought the functional importance of EV-miRNAs, especially sEV-miRNAs has gained some support, including in the area of immunologic response and metastatic tumour cell growth [60]. In addition to exercising their function intracellularly, miRs can also be exported from cells in the extracellular space via EVs or bound to proteins such as Ago-2 or HDL (Figure 1) [61].

All neural cells from rodent and human microvascular endothelial cells, even immortalised human brain, release EVs containing mRNA and miRs for epigenetic

reprogramming of neural cells or post-transcriptional control of specific genes. When several types of miRs are isolated from cerebrospinal fluid, such as miR-100, miR-146, miR-505, and miR1274a they are expressed differentially in AD. There is a correlation with the neuropsychological assessment and brain imaging in the presence of several types of serum - isolated exosomal miRs (miR-361-5p, miR-93-5p,miR-335-5p and miR-305p) [62].

The contribution of exosomes in neurodegenerative diseases, particularly in Alzheimer's and Parkinson's diseases, is most studied (within) 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 central nervous system (CNS) pathological processes [63]. Vesicles can in 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 in 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 [64]. 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 an action potential [65]. 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 [63].

EVs actually interact with target cells which cause phenotypic changes in them. For these reasons, EVs are now seen as leading intercellular communication actors, mediating both physiological and pathological responses. Additionally, EVs can activate intracellular pathways in target cells through ligand-receptor interactions or EV membrane proteins can be proteolytically cleaved by proteases [66, 67].

miRNAs can be effectively transported by EVs and perform their molecular function regularly in recipient cells. ATP-binding cassette transporter A1 (ABCA1) may participate in High-density lipoproteins (HDL) miRNA export mechanism. Confirming that endogenous levels of HDL-supplied miRNAs are adequate to affect gene expression in target cells [68, 69]. HDL-associated miRNAs can be transported into cells by moving a particular receptor to the cell membranes of the receiver [70].

In conclusion, as with other scientific disciplines, EV science is moving forward by a combination of new ideas, technologies, astute observations, and careful data analysis. More

specific and standardised purification methods are also needed to incorporate EVs as biomarkers, vaccines, or drug delivery devices in a clinical environment.

Role of extracellular vesicles in the nervous system

As mentioned before, extracellular vesicles (EVs) is a term used to describe lipid-bilayer particles that are released from the cell and cannot replicate [71]. They are classified into three subtypes according to their size and their mode of biogenesis into, apoptotic bodies, microvesicles and exosomes [72]. They are responsible for intercellular communication that are involved in different physiological and pathological conditions [73]. In the nervous system, EVs have a role both in healthy conditions to maintain the central nervous system (CNS) development, and in 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 [64].

Under normal physiological conditions, exosomes released from various glial cells (astrocytes, oligodendrocytes, and microglia) maintain the adult brain and CNS development, such as regulating the synaptic activity and regeneration after injury; also these exosomes interact with neurons for the development and maintenance of the neural circuit via promoting neurite outgrowth from hippocampal and increase in the survival of cortical neurons [64]. Whereas, neural exosomes involved in the elimination of synapse and stimulation of microglial phagocytosis are also responsible for controlling the communication with glial cells [64].

The function of Astrocytes-derived EVs:

Astrocytes are the most common type of glial cells within the CNS that play various roles in the healthy nervous system starting from supporting and maintaining the homeostasis at the synapse, signalling regulation, controlling the blood flow, maintaining the blood-brain barrier (BBB), and protecting neurons against oxidative damage [74]. In addition to their roles in regulating the concentrations of neurotransmitter and ions, trophic factors' production, maintaining the redox potential, and toxin and debris elimination from cerebrospinal fluid (CSF) [75]. While in brain injury and infection, they act as reactive immune cells and mediate inflammatory response through recruitment, instruct and restrict the immune and inflammatory cells at the injury and diseased sites [76]. In CNS, EVs are considered as a non-synaptic mode of communication contributing to the diffusion of signalling and brain codification [77]. Different studies illustrated that astrocytes secret exosomes into the culture medium under different conditions [78-82].

Venturini and colleagues found that astrocytes-derived exosomes targeted neurons in the neuron-astrocytes network and carrying neuroglobin (NGB) a protein that functions as anti-oxidant, anti-apoptotic, and anti-inflammatory, thus can act as neuroprotectant; moreover, their exosomes could contribute in signal transmission and by volume transmission they could travel near or long distances to hit the targets [83]. Another study found that microvesicles released from astrocytes transfer mitochondrial DNA (mtDNA) between cells; and these microvesicles were identified as exosomes by the presence of protein markers, such as ALIX, CD9 and TSG10 [78]. 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 [84]. 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 [85].

The function of Oligodendrocytes-derived EVs:

Oligodendrocytes are the myelinating cells of the CNS, arise from oligodendrocyte progenitor cell (OPC). Oligodendrocytes play a crucial role in myelin generation [86] required to enwrap axons to promote fast saltatory conduction of action potentials, also provide metabolic support to the axon, and contribute to neuroplasticity [87]. Like astrocytes, oligodendrocytes release exosomes as a result of neurotransmitter glutamate stimulation through ionotropic glutamate receptors, 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), in addition to RNA are taken up by neurons through endocytosis [88]. Fröhlich and colleagues found various roles of oligodendrocytes-derived exosomes on neuron physiology; these exosomes increase the firing rate of the neurons action potential, activate the signal transduction pathways of the cells and change their transcriptome. Furthermore, *in vitro* model of cerebral ischemia were used to study oligodendrocyte-derived exosomes understroke condition which has neuroprotective effect by transferring protective proteins, for example, catalase and superoxide dismutase (SOD) [89]. Another study illustrated the exosomes that are delivered from oligodendrocytes influence axonal homeostasis and long-term maintenance [90].

The function of Microglia-derived EVs:

On the other hand, 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 [91]. Along with CNS-infiltrating macrophages act as a scavenger that facilitates removal of aged, necrotic tissues and damaged neurons and synapses [92]. Also, neurotrophic factors, such as insulin-like growth factor is released by microglia to support neural survival and differentiation during postnatal development [93].

Microglia release exosomes under serotonin stimulation as explained by Glebov et al., study; they found that under physiological conditions, serotonin released from neurons could stimulate the serotonin receptors (5-$HT_{2a,b}$ and 5-HT_4) on microglia to release exosomes [94]. While the proteomic analysis of microglia-derived exosomes isolated from the murine brain showed a number of enzymes, chaperones, tetraspanins and membrane receptors similar to exosomes derived from the dendritic cell and B cell. Aminopeptidase CD13 and monocarboxylate transporter's expression considered unique and used to distinguish them from other hematopoietic cells [95]. Also, microglia stimulated by ATP secrete EVs that have a set of proteins required for cell adhesion/organisation of extracellular matrix, degradative pathways and metabolism of energy, and promote few activation markers expression in the recipient astrocytes [96].

The function of Neuronal-derived EVs:

Exosomes are released from neurons 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 [97, 98]. In addition to exosome markers, they carried subtypes of glutamate receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), miRNAs associated with neurite, for example, miR-124 and miR-1973, also microtubule-associated protein 1B. Thus, neurons-derived exosomes play a role in exporting miRNA, modulating the excitability of neurons, and neurotransmitter release [91]. Sharma and colleagues illustrated the role of neuronal exosomes in the development of neural circuit that leads to enhance the proliferation of neural progenitor, neuronal differentiation, and circuit connectivity [99]. Another study found that neuronal exosomes regulate synaptic pruning via microglial phagocytosis stimulation; incubation of the rat pheochromocytoma PC12 cells exosomes with microglia led to increasing complement component 3 (C3) expression level that enhanced the microglial phagocytic activity [100]. All these studies provide examples of the role of exosomes in cell-cell and glial-neuronal communications in maintaining CNS homeostasis.

Role of EVs in neurodegenerative diseases:

EVs are released by glial cells and neurons; they considered a mean to assemble and transport proteins that could contribute to healthy CNS development and also transport neurotoxic proteins that could participate in developing neurodegenerative diseases, such as Alzheimer, Parkinson, amyotrophic lateral sclerosis, Huntington, and prion diseases (Figure 2).

Alzheimer's disease

AD is the most common and major type of dementia. It characterised by a reduction in memory cognition and executive function which hinders daily life. According to WHO, about 50 million people have dementia, and 60-70% of cases are contributed to Alzheimer disease in the world and it is predicted that this figure would double every 2 years . However, The primary cause is still unknown, but the widely accepted causes are β-amyloid (Aβ) peptides accumulation, intracellular neurofibrillary tangles formation that consist of hyperphosphorylated tau protein [101].

Genetically, the apolipoprotein E (APOE) ε4 allele is the most important risk factor for late-onset AD [102]. 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. However, in patients with AD, the frequency of the ε4 allele is dramatically increased to ~40% [103]. A 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 which indicate a new role of exosomes in the pathogenesis of AD [104]. 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 [105]. Apoptosis could be induced by astrocytes surrounding amyloid plaques by caspase 3 activation; this his 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 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* [81]. Studies found that inhibition of exosomal secretory pathways and synthesis of exosome in microglia could stop the propagation of tau and a load of amyloid plaque *in vitro* and *in vivo* [106, 107].

As microglia has a role in tau pathology [108], Asai and colleagues found in the mouse model that depleting microglia halts tau propagation and decrease excitability in the dentate gyrus; in addition to inhibition of the synthesis of microglia-derived exosomes both *in vitro* and *in vivo* [106]. Results from this study suggested that propagation of tauopathy could be caused by microglia and exosomes [106]. A study by Crotti et al., showed that Despite Bridging Integrator 1 (BIN1) which is 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, exacerbate the *in vivo* Tau pathology in PS19 mice [109].

A 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 [110-113]. Specific microRNAs have also been shown to play a key role in regulating the expression of APP and BACE1 which restricts the development of Aβ. Accumulating evidence shows that increased APP expression can promote Aβ development, leading to neurotoxicity, synaptic failure and ultimately dementia [114]. 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 [115]. AD is one of today's most common neurodegenerative disorders, but sadly there is currently no treatment available [116]. Studies on microRNAs in AD have provided influential 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 and other dementias can improve quality of life for people with dementia and their caregivers through all stages of the disease [117, 118].

Parkinson’s disease

PD is the second common neurodegenerative disease, caused by a decrease of dopamine level in the brain due to dopaminergic cell death [119]. The incidence of PD increases with age and affects 1 to 2 people per 1000 at any time [120]. The worldwide incidence ranges from about 5 per 100,000 to over 35 per 100,000 new cases every year [121]. The most common clinical and pathological hallmark of PD is the aggregation of α-synuclein (αsyn) protein which is one of the Lewy bodies components; also it is a presynaptic protein that binds small synaptic vesicles and has dopaminergic neurotoxicity [63].

According to a study by El-Agnaf and colleagues α-synuclein was detected extracellularly in human plasma, in CSF and also in the culture media of α-synuclein transfected and untransfected human neuroblastoma cells [122]. Another study explained that α-synuclein is secreted by exosomes by calcium-dependent mechanism and thus could propagate PD [123]. Alvarez-Erviti group showed how exosomes responsible for transporting α-synuclein from affected to healthy unaffected neurons via using SH-SY5Y cells, and also found that lysosomal dysfunction increases the exosomal transmission of α-synuclein to cells [124]. The type of α-synuclein that is present in exosomes and is considered to be more toxic to neighbouring cells is αsyn oligomers, as explained by the Danzer group's study. Also, they found that autophagy is the mechanism used for αsyn oligomers degradation; thus, disruption of the mechanism could lead to increase exosome-associated αsyn oligomers [125]. A recent study found that αsyn oligomers' exosomes present in the saliva of PD patients and the ratio of αsyn oligomers to total αsyn is higher in PD than in healthy controls; thus they suggested that salivary exosomes might be useful as a diagnostic biomarker for PD patients than plasma [126]. Chang and colleagues studied the microglial-exosomes from α-synuclein-induced mouse and found that the number of exosomes secreted from activated microglia was much higher compared to the control group; also these exosomes showed a high expression level of MHC II and mTNF-α and could induce abnormal apoptosis of neurons [127]. Thus these mechanisms could play a role in the pathogenesis of PD and might be a target for therapeutic approaches [127].

As mentioned by different studies that α-syn aggregates 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 [128]. While another study used catalase-loaded exosomes, were catalase is a potent antioxidant to treat PD [129].

Extracellular miRNAs are fairly stable as they are secured against degradation by binding to RNA-binding proteins and/or packaging into exosomes [130]. miRNA dysregulation may lead to the development of different diseases from brain disorders to cancers [131, 132]. Indeed, several studies have shown that the miRNAs expression profile is dysregulated in PD, and can lead to pathogenesis of PD [133] (Table 2). miR-34b and miR-34c have been shown to be downregulated in patients with PD and specifically in amygdala, SNpc, frontal cortex and cerebellum, combined with a substantial decrease in PARKIN and DJ-1 protein concentrations [134]. *PRKN* and *PARK7* genes, encoding for the PARKIN and DJ-1 proteins respectively, are both associated with autosomal recessive PD pathogenesis [135]. 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 the activity of ubiquitin-protein ligase, suggesting that *PRKN* mutations cause PD insurgence [136, 137]. PD is a significant neurodegenerative disorder, the prevalence of which increases with ageing. Understanding the dynamics of miRNA control in the brain represents a crucial goal and a very common topic in biomedicine, with significant implications for elucidating the pathophysiology of major neurodegenerative diseases, like PD [133].

Prion disease

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 alpha helix (42%) and a few beta sheets (3%) [138]. 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 [139]. During the early 1920s Creutzfeldt-Jakob disease (CJD) was first described [140, 141]. 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 in young age (in the 30s or 40s), but also in later life [142, 143]. Many of all human prion diseases (75%) were classified as sporadic CJD (sCJD), associated with rapid development of the disease, multifocal dementia, tiredness, insomnia, and depression [144]. Typical clinical symptoms include progressive dementia, accompanied by abnormalities in the visual and cerebellum function, myoclonia, pyramidal and extrapyramidal dysfunction or acinetic mutism [145]. Approximately 85–90 percent of cases of CJD occur sporadically and affect 1–1.5 persons per million per year [146]. Little is known about the pathogenesis of sporadic CJD (sCJD). Given that there are no specific therapeutic and prophylactic interventions available for prion diseases, active surveillance is critical to the control and prevention of human prion diseases, particularly those caused by animal-derived prion agents [138].

According to medicine, prion diseases are unusual in that they can occur by three mechanisms: random (sporadic), hereditary (family), and acquired (infectious / transmitted). The prion disease model is that PrP^{Sc}, the pathologic disease-causing misfolded form of the prion protein, acts as a template, so that it transforms PrP^{C} into PrP^{Sc} when it comes into contact with a prion protein, PrP^{C}, resulting in two prions [147]. Prion diseases occur in humans as a sporadic, genetic, and transmissible illness. To date, more than 40 different PrP gene mutations

have been demonstrated to segregate with the heritable human prion diseases [148, 149]. The resulting diseases have been classified according to clinical symptoms as Gerstmann – Sträussler – Scheinker syndrome (GSS), Creutzfeldt-Jakob disease **(**CJD), or fatal family insomnia (FFI), although all result from prion protein (PrP) encoding gene, PRNP mutations [150].

The fatal neurodegenerative disorders of human prion diseases, also named transmissible spongiform encephalopathies result from the conformation of a normal cellular prion protein (PrP^{C}) to an abnormally misfolded pathological (PrP^{Sc}) form [140, 141]. PrP^{Sc} accumulation leads to the onset of transmissible spongiform encephalopathies, which attack the central nervous system, leading to progressive neuronal degeneration and neuronal vacuolation [151].

The human prion protein (PRNP) gene, is located in humans on chromosome 20p12 [152]. In the inherited type of the disease, a genetic mutation in the PRNP gene can induce a change in PrP^{C} conformation [153]. These mutations include point mutations in the PRNP sequence, and repeat insertions or deletions of octapeptides in the N-terminus of PrP. Several epidemiological surveys report a lack of definite family history in certain patients with genetic prion diseases [154]. Many variants have been identified in the PRNP gene, the pathogenic existence of which has not been explained [155]. M129V and E219K are fairly common PRNP gene polymorphisms, and are complicated in their pathogenic nature [156]. In sCJD, iatrogenic CJD (iCJD), and classical CJD (cCJD), M129V are suggested to play a role [156].

The PrP open reading frame (ORF) is encoded inside a single exon in all identified PrP genes of different species, while the gene itself contains two to three exons [150]. The other exons include untraduced sequences including the sites of the promoter and termination [150]. To date, more than 40 different PrP gene mutations have been demonstrated to segregate with the heritable human prion diseases [150].

Kuru is the first human prion disease that has been shown to be transmissible to chimpanzees through intracerebral introduction of kuru-patients 'brain homogenates [157]. Also, in 1955 Frank Earl, an emergency physician who accompanied Colman, identified the disease and proposed that kuru may be a type of encephalitis [158, 159]. In the 2000s after the discovery of kuru, Gajdusek said that only fully intoxicated will come to the conclusion that cannibals would transmit a disease endemic by eating bodies. According to Gajdusek, the theory was taken for granted, but it is also true that he said in his Nobel Prize lecture that kuru spread through conjunctival, nasal, and highly infectious brain tissue contamination [160]. Kuru has three clinical stages in the infected individual, namely ambulance (the person can still walk), sedentary (the person can only sit up), and terminal (the person cannot sit up

independently). These stages may be preceded by an underdefined prodromal period characterised by headache and pain usually in the joints of the legs [138]. Numerous kuru plaques, spherical bodies with a rim of radiating filaments, are the neuropathological property which distinguishes kuru from sCJD. Kuru is thought to be caused by the use of a sCJD case and experimental transmission studies have shown similarity between the molecular and pathobiological properties of prions that cause kuru, sCJD and iCJD [161].

Several miRNAs are expressed selectively in the central nervous system (CNS) and were reported to be involved in the growth, function and pathogenesis of CNS [162]. The study of miRNAs with relation to prion pathogenesis has gained experimental traction as many miRNAs have been shown to be altered in *in vivo* and *ex vivo* models of prion diseases [163] (Table 3). A possible association between miRNAs and prion diseases was suggested based on the co-location of PrP^C in endosomes and multivesicular bodies within 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 [164].

Prion diseases arise when normal prion protein, which is present on several cells surface, is irregular and clumps inside the brain, causing brain damage. Prion diseases are lethal mammalian neurodegenerative conditions and increasing every year. There is no cure for these diseases as yet. The biggest problem with prion diseases is that the condition is still unrecognized. Therefore, the future research of prion disorders with miRNAs could provide further information for diagnostics and targeted therapy of other neurodegenerative diseases.

Huntington's disease

In 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 that goes from generation to generation within families starting in the middle ages and is characterised by excessive choreographic gestures, behavioural and psychiatric disorders and dementia [165]. It is 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 [166].

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 an change in the number of repetitions of three nucleic acids (C, A, and G) in the first HD gene exon's coding region [167]. The CAG trinucleotide repeat is usually repeated about 20 times,

but an estimated doubling of the number of repetitions to 40 or more results in the disease expression [168]. HTT protein is commonly distributed in the central nervous system (CNS) and other non-neuronal tissues and spreads across the compartments and in human HTT protein is a large protein with a molecular weight of 350 kDa (3144 aa) [169].

Expansions of CAG may mediate neurodegeneration through an abnormal expansion of polyQ and an inductive 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 [170].

Normal HTT is important for brain growth; HTT knock-out mouse embryos have significant defects in the development of the central nervous system and die soon after birth [171]. In addition, HTT is expressed during development in the brain and plays a crucial role in survival and cohesion of the neurons [172]. Moreover, HTT is important for the neural induction programme, progressive selection of neural progenitor cell types and subsequent creation of neural lineage organisms [173].

HD is characterised by widespread mis-regulation of mRNA, especially in striatum and cortical regions [174]. This deregulation is partially the result of aberrant nuclear localisation of the RE1-Silencing Transcription Factor (REST) transcriptional repressor [175, 176]. According to recent studies, 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 [177, 178]. 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 main members of the RNA-induced silencing complex (RISC) with the possibility that small-RNA silencing-dependent mechanisms may be involved in HD neuropathology [179].

The HD Research Crossroads database nowadays contains information around 800 genes for which the available evidence suggests a direct or indirect significance to HD pathophysiology. Therefore, these genes may be considered as targets for therapy production, which is a prime objective of HD research. The goal information is collected by the evaluation of existing studies and in-house screens [180].

Sadly, there are currently no effective therapies for HD which change the disease. The latest accepted treatments are only symptomatic, and do not change the course of the disease [181]. Within each mechanistic category, treatments approved by FDA are classified first (A),

followed by those showing promise in human studies (B), followed by those failing in human studies (C), and lastly, treatments with convincing evidence in rodent or cell models (D) [182].

MiRNAs have recently been found to have an aberrant expression or deregulation that plays a major role in the pathogenesis of many Poly Q diseases [183] (Table 4). A large number of studies using different human samples have recorded aberrant miRNA expression in HD by applying RNA sequencing, microarray, and qRT-PCR techniques [184]. A large number of HD cell models and animal studies have shown in recent decades that miRNAs can affect the pathogenesis, progression, and prognosis of patients through various pathways [177]. 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, they conclude the miR-128 may play a pivotal role in HD pathogenesis [185]. 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 [186].

As indicated above polyQ disorders, especially Huntington's disease is a debilitating illness mentally, psychologically in the world. The genetic mutation causing all of the HD results in an irregular expansion of a polyQ tract in the HTT protein. Huntington disease is not yet fully understood.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a lethal neuronal motor disease that is 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 [187, 188]. Given the poor prognosis, the survival rate varies significantly and up to 10 percent of people with ALS have been surviving from the first symptoms for more than 8 years [189]. It is still unclear what causes ALS. Notable progress has been made in identifying the disease's genetic and environmental components [190].

The French neurologist Jean-Martin Charcot coined the term "amyotrophic lateral sclerosis" in the 1800's: "amyotrophic" refers to muscle atrophy, and "lateral sclerosis" describes the scarring or hardening of tissues in the lateral spinal cord. The key neuropathological symptoms of ALS are extensive loss of lower motor neurons from anterior spinal cord and brain stem horns [190, 191]. The most common signs of ALS are muscle fatigue, twitching and cramping, which can ultimately lead to muscle failure [192, 193]. Symptoms of dyspnea and dysphagia may develop in ALS patients at the most advanced stages

[194, 195]. Other prominent ALS symptoms are fatigue and a decreased capacity for exercise [196]. When the illness progresses, patients need routine core tasks to assist [196].

Actually, 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) [197, 198]. French neurologist Jean-Martin Charcot first identified ALS in 1869, then the disease became well known in the United States when baseball player Lou Gehrig was diagnosed with the disease in 1939 [199].

Partly since ALS demonstrated great clinical variation in presentation and prognosis, diagnosis may be difficult at an early stage [200]. Since ALS is a disabling and life-threatening illness, misdiagnosis can have serious implications for patients and carers [201]. 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 1993 the first gene of ALS, cytosolic superoxide dismutase or SOD1, was identified [202]. In most ALS cases, a protein named TDP-43 is the primary component of these aggregates including cases induced by repeated expansions of C9orf72 [203, 204]. It is thought that the penetration of C9orf72-related ALS by the age of 80 is nearly 100 per cent. 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 length of the disease are theoretically unknown [205]. The repeat expansion of C9orf72 may be correlated with aberrant RNA metabolism due to the sequestration of RNA binding proteins, the development of abnormal RNA species or the formation of increased DNA instability [206]. 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 [207].

Dysfunctional mitochondria contribute to impaired neuronal energy production and eventually results in neuronal cell death [208]. In neurodegenerative diseases, especially in ALS is the key marker of mitochondrial dysfunction [209]. ALS transgenic mice (SOD1G93A) reveals its effectiveness against ALS-related neuronal cell death (anti-apoptotic) and stabilisation of mitochondria by *in vivo* investigations affecting the PI3K-AKT signalling pathway [210]. 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 [211]. Some researchers have demonstrated low levels of these transporters in ALS patients 'spinal cord and cortex due to aberrant EAAT2 mRNA transcript synthesis and altered expression of EAAT2 causes glutamate to increase, leading to death and degeneration of the motor neurons [212].

ALS contains misfolded proteins, such misfolded proteins 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 [213].

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 [214] (Table 5).

It has been proposed that many distinct neurological disorders including Parkinson's disease (PD), frontotemporal dementias (FTD), and ALS have common environmental and genetic susceptibilities [215, 216]. Additionally, due to their tau hyperphosphorylation, work has indicated a correlation in the etiology of both Down syndrome and SOD1-related ALS disease. Better understanding of how these mechanisms are related may play a key role in improving patient care and management [217]. ALS and FTD share similar genetics and exist on the same continuum of pathologies. Clinically, it is now known that up to 50% of ALS patients have a degree of cognitive or behavioral disability and up to 33% of FTD patients have evidence of interference with motor neurons [216, 218, 219].

Extracellular vesicles bear donor cargo to recipient cells. Mutant proteins causative in ALS were recovered in EVs and transmitted via the brain cells as a way of transmitting the disease[220]. SOD1 is an abundant enzyme, or superoxide dismutase one, which transforms superoxide molecules into hydrogen peroxide and dioxygen. SOD1 was the first ALS-associated protein identified in EVs from healthy neuron-like mouse motor (NSC-34) cells that over-expressed human wild-type and mutant SOD1 [221]. Grad and his colleagues further characterized the aggregation state of mutant SOD1 in EVs and indicated that misfolded SOD1 in EVs lead to the prion-like spread of pathology in the CNS [222]. Many studies have examined miRNA in ALS patients with CSF, urine, serum or plasma, but no biomarkers are yet available for this condition, possibly due to the technical variation in circulating miRNA analysis [222].

Dysregulation of the RNA pathway actually seems to be a significant contributor to ALS etiopathogenesis. C9ORF72 mutations are the most common gene associated with ALS, resulting in toxic mRNA gain in function through the formation of RNA foci, and subsequent sequestration and altered behaviour of RNA-binding proteins (RBPs) [223]. TDP-43 and FUS is active in the synthesis of miRNA [224]. For example, TDP-43 and FUS facilitate miRNA biogenesis by interacting with Drosha and Dicer, two primary enzymes used to transfer miRNAs from precursors to mature molecules [225, 226]. Mutations in TDP-43, FUS, and SOD1 activate a stress response pathway leading to generally decreased levels of miRNA most likely contributing to motor neuron (MN) degeneration [227]. ALS is a motor neuronal disorder and it has been shown in numerous studies that ALS can be caused by miRNA dysregulation and thus protein expression in the cells. In ALS, reduced pre-miRNA processing and decreased levels of various miRNAs are caused by the remodelling in cytoplasm of the Dicer complex [228]. ALS can come from a variety of causes as genetic, epigenetic, environmental and internal. ALS is a consistently a lethal condition and rapid improvement in our understanding gives us hope that this debilitating disease can be handled effectively.

Multiple sclerosis

Multiple sclerosis (MS), the most common neurological disease, is an autoimmune-mediated condition affecting the central nervous system (CNS) and sometimes leading to significant physical or cognitive impairment and neurological disorders in young adults [229]. MS targets the myelinated axons in the CNS, killing to various degrees the myelin and axons [230]. The [231]cause is unclear, but it appears to include a combination of genetic susceptibility and a non-genetic trigger, 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. Approximately, 2.5 million people in the world are affected by MS with young people between the ages of 20 and 40 most affected [232]. The higher prevalence of MS is seen in women who suffer twice as much as men [233]. 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 [234]. MS is considered to be the most common cause of neurological impairment, because MS-related inflammatory lesions can affect a wide variety of systems to varying degrees and cause a multitude of neurological symptoms and comorbidities. Those include sensory impairment, visual confusion, double vision, muscle weakness, ataxia and impaired balance, which can dramatically decrease the quality of life of people affected [235, 236]. MS is difficult to handle and requires many medications working

through various pathways. The diagnosis depends fundamentally on the nature and form of the disease [237].

MS targets the myelinated axons in the CNS, killing to various degrees the myelin and axons [238, 239]. 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 (PRMS). RRMS is the most common subtype (about 87%) with sporadic acute attacks accompanied by periods of remission [240].

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 play an important role in the initiation and progression of MS [241, 242]. 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 [243]. Such cells mediate suppression and inactivation of $CD4^+$ T cells through the development of cytolytic proteins such as perforin. In addition, these cells extensively increase vascular permeability, kill glial cells and cause oligodendrocyte death plays a significant role in MS pathogenesis [242].

EVs exhibit both defensive and harmful roles in MS pathogenesis. EVs may, in addition, be considered helpful during neurological processes by restoring trophic factors, removing damaged cells, regulating synaptogenesis, and monitoring the functional status of synapses as mentioned above [244-246]. We have recently recorded a high number of microvesicles produced by monocytes of MS patients compared to healthy donors [247]. 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 [70, 248-251] (Table 6). Extracellular vesicles play important roles in MS growth, in particular by stimulating cells during relapses, leading to migration through the BBB, and spreading inflammation in CNS tissue. At the other hand, a protective effect of EVs was identified with the induction of oligodendrocyte precursor cells maturing and migrating [252].

miRNA expression has been dysregulated in various immunological diseases, such as MS and others [253]. Some researchers have shown that miRNAs can contribute to the development of MS and to treatment responses [254]. Multiple sclerosis (MS) serves as an example of a chronic and organ-specific autoimmune syndrome in which miRNAs modulate

immune responses in the peripheral immune compartment and the neuroinflammatory cycle throughout the brain [255]. miRNAs are also involved in adult neurogenesis that can suggest the possible role of some miRNAs in endogenous repair mechanisms in MS [256]. 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 [257]. Genetic predispositions combined with environmental factors play a significant part in the pathogenesis of multiple sclerosis. MS is a chronic disease so far without cure and the exact cause of MS is still unknown. Therefore, this review for a detailed study of the MS in genetic context will be crucial way.

Role of trinucleotide repeats in neurodegenerative diseases

Microsatellites are generally defined as simple sequences of 1-6 nucleotides repeated multiple times, and present in the genome's coding and non-coding regions. Repetitive sequences are well represented in the eukaryotic genome and are reported to be recombination hot spots as well as random integration sites [258-260]. Repetitive sequences make up 30% of the human genome and are often deleted and inserted sites. The incidence of repetitive elements is significantly higher than that of random sequences of the same base composition, and the various microsatellites are represented at different frequencies in the genome. For example, in all eukaryotes, repeats of di - and tetranucleotides are more abundant than repetitions of trinucleotide repeats (TNR) [261].

Simple TNRs have taken on special significance in this regard, as genomic amplification of TNR is the underlying genetic defect in a number of human diseases, including neurodegenerative and neuromuscular diseases and mental retardation [262]. Simple DNA repeat expansions underlie ~20 serious neuromuscular and neurodegenerative disorders. Although our understanding of pathogenic mechanisms for expansion diseases of TNR has advanced significantly in recent years, but many aspects of the mutational mechanism remain enigmatic [263].

Five other neurological diseases caused by untranslated triplet repeats found in the 3′(myotonic dystrophy), the 5′(fragile XE mental retardation and spinocerebellar ataxia (SCA) type 12), the intronic Friedreich ataxia (FRDA) and even potential antisense sequences (SCA type 8 (SCA8)) were identified in the following years [264]. In addition, it is now known that seven other neurodegenerative diseases result from the expansion of (CAG)n repeats coding for polyglutamine tracts in the respective proteins: Huntington disease (HD), Dentatorubral-pallidoluysian atrophy (DRPLA), and SCA types 1, 2, 3, 6, and 7. In general, repeat disorders

of trinucleotides are either dominantly inherited or X-linked, with the one exception being FRDA, which is autosomal recessive [265].

Neurodegenerative disorders are caused by a wide array of genetic mutations and epigenetic and environmental factors, and repeat expansion of trinucleotides is increasingly recognised as the cause of many neurodegenerative diseases. To date, more than thirty neurological and neuromuscular diseases account for trinucleotide repeat expansions [266]. Pathogenic expansions may occur in gene coding or noncoding regions. In disorders such as Huntington's disease (HD) and six spinocerebellar ataxias (SCA1, 2, 3, 6, 7, and 17), expansions of trinucleotides in the protein-coding region result in the synthesis of expansions of polyglutamine (poly Q), which accumulate in ubiquitin-positive inclusions and interfere with cellular homeostasis, leading to cellular homeostasis [266]. In different intragenic the non-coding repeat expansions involve different sequence motifs. For example, the expansion is a repeat of CGG in fragile X mental retardation 1's 5′ untranslated region (UTR) in fragile X syndrome, a repeat of GAA in Frataxin's first intron in FRDA, and a repeat of CTG in DMPK's 3′ UTR in myotonic dystrophy type 1 [267].

Polyglutamine diseases constitute a representative and largely studied group of neurodegenerative disorders in which significant amounts of data were collected on the role of expanded polyQ in pathogenesis of diseases [268]. More than 20 years ago, the finding that the expansion of CAG repeats in the androgen receptor gene coding sequence was the genetic basis of Spinobulbar Muscular Atrophy was a hallmark in the discovery of these novel dynamic mutations and their association with human disease. A few years later, the identification of intracellular inclusions containing the expanded proteins provided an indication of pathogenesis, leading field research into extensive research into the mechanisms of aggregation of polyQ-induced proteins [269].

Neurodegenerative syndromes have been associated with the following triplets (when present on the coding strand): CAG, CTG, GAA, CCG, and CGG. Most exhibit a negative correlation between repeat length and disease onset and/or disease progression severity [270]. There is convincing evidence that RNAi-active small RNAs can be formed by CAG / CUG TNRs. In human neuronal cells, expression of the CAG expanded HTT exon 1 (above the threshold for complete penetration which is > 40) caused an increase of about 21nt in length of small CAG repeat-derived RNAs (sCAG). The CAG / CUG repeats were found to be cleaved by Dicer over a certain length and have RNAi activity. To be cleaved by Dicer, a TNR sequence must form a hairpin stem structure which is similar to a miRNA. CNG-type TNRs (CAG, CUG,

CCG and CGG) have been shown to be capable of forming stable hairpins which Dicer can cleave [271].

miRNAs are abundant within the central nervous system (CNS), as brain-specific miRNAs assist in various neuronal processes such as synaptic development, maturation, and plasticity [268, 269]. Altered miRNA expression has been observed in CNS diseases, especially age-dependent neurodegenerative diseases, suggesting that miRNA expression may contribute to neuropathogenesis. In HD, miRNAs dysregulation was reported in HD in vitro models, transgenic HD animals, and the human HD brain [272].

The problem of predicting miRNA binding sites with messenger RNA (mRNA) has arisen following the discovery of the important role of miRNAs (miRNA) in regulating gene expression. Several programs that predicted binding sites to miRNA were created. Yet, when searching for binding sites, many of them had unreasonable restrictions. Using some bioinformatics programs like MirTarget program to identify binding sites of miRNAs with mRNA genes having nucleotide repeats. The program identifies the initiation of miRNA binding to mRNA, the localization of miRNA binding sites in mRNA regions, and the free energy from the binding of all miRNA nucleotides with mRNA. The MirTarget program found hydrogen bonds between adenine (A) and uracil (U), guanine (G) and cytosine (C), G and U, and A and C [273].

According to the results of the MirTarget program some studies have identified the binding sites of miRNAs with mRNA genes to have trinucleotide repeats. For example, in the coding regions the count of 2567 human miRNAs and their binding sites with 102 mRNAs of human genes having nucleotide repeats has been fulfilled. From these results, the binding sites of miR-1181 and miR-1908-3p in mRNA of *ATXN7* and *ZIC2* genes interact with free energy more than -112 kJ/mole. There trinucleotide repeats of (CGG) located between 599 and 670 nucleotides in the *ATXN7* gene and miR-1181 bind in this region with a start at 593 nt. Trinucleotide repeats of (CGG) in the *ZIC2* gene repeat between 1786 to 1816 nt and miR-1908-3p binding sites located from 1787 nt (Table 7) [274].

Current developments in Stem cell 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 [275]. It is not only possible to postpone the progression of incurable neurodegenerative diseases such as PD, AD, and HD thanks to stem cell therapy, but also, most significantly, to eliminate the source of the problem [276].

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 [277]. Pluripotent stem cells have not yet been used therapeutically in humans because several of the early animal experiments have resulted in the undesirable development of rare solid tumours, called teratomas, made up of a mixture of cell types from all early germ strata. Animals were successfully treated with cells originating from pluripotent cells [278]. There has also been substantial progress in identifying the transcriptional circuitry and the epigenetic modifications associated with pluripotency [279]. This research area is moving very rapidly as a result of tremendous advances in DNA sequencing technology, bioinformatics and computational biology. The main pluripotency transcription factors also regulate the microRNAs involved in controlling self-renewal and differentiation of ES cells, again positively and negatively [280].

Multipotent stem cells harvested from the bone marrow were used to treat leukaemia, myeloma and lymphoma since the 1960s. Recently some progress in the use of bone marrow-derived cells to treat certain diseases has been identified [281]. 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 [282]. Clinical experiments of dopamine neurons derived from stem cells have undergone a new and groundbreaking age in stem cell treatment for PD. Guidelines and guidelines for clinical translation to patients were then set [283, 284].

Despite the long-term emphasis on AD diagnosis, there is still no successful therapy which can interrupt or reverse the disease progression [285]. Stem cell therapy was first conducted on animal models as an approach to treat AD [286]. Neural stem cells originating from the hippocampus of neonatal rats were implanted in the brain of AD rats and were able to develop into the new cholinergic neurons enhancing spatial learning and memory capabilities of AD rodent models [287]. While stem cells hold great promise in therapeutics, scientific evidence on the safety and efficacy of their use is needed [288]. 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 big obstacle to be addressed [289].

Mesenchymal stem cells (MSCs) are a group of non-hematopoietic adult stem cells that derive from the mesoderm, also called mesenchymal stromal cells [290]. MSCs have been shown to possess the capacity to differentiate into a range of cell types, including adipocytes,

osteoblasts, chondrocytes, myoblasts and neuron-like cells, as typical multipotent stem cells [291]. 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; [292, 293]. There is currently a great deal of interest in the use of MSCs in pioneering therapies for the treatment of chronic and progressive neurodegenerative diseases which are currently incurable and whose attempts to find disease-modifying therapies such as AD, PD, ALS and HD have failed [294]. Furthermore, MSC-induced functional recovery from stroke and brain injury is not due to MSCs that replace damaged neurons, but rather to MSCs that induce growth factor production and promote intrinsic neurorestorative brain functions [295-297]. Exogenously administered MSCs can selectively target damaged tissue by a homing mechanism, interact with brain parenchymal cells, reduce the expression of axonal inhibitory molecules [298]. In addition, the MSCs can stimulate the development of positive growth and plasticity factors that increase neuritis outgrowth, promote neurological restauration and recovery after brain injury [298]. Administration of MSC-derived cell-free exosomes is sufficient to exert similar therapeutic effects to intact MSCs following brain injury [299]. Functional miRNAs transferred from MSCs to neural cells through exosomes promote neurite remodelling and functional recovery in a co-culture stroke rat model [300]. 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 [301]. Exosomes derived from MSC may transfer proteins and RNAs to recipient cells and may have several effects on the growth of different tumour cells [302] (Table 8). MSCs generate exosomes that can perform as paracrine mediators by transferring signalling molecules that regulate tumour cell proliferation, angiogenesis, and metastasis via a number of regulated cellular pathways [11, 303]. 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 proprieties [304].

Untreatable neurodegenerative diseases currently have the potential to become treatable with stem cell therapy. Stem cell research helps scientists understand how an organism grows from a single cell, and how healthy cells in humans and animals replace damaged cells. This procedure could also reverse the ageing process, which is a natural phenomenon. Also, the use of these cells will truly open the way to personalised medicine in future clinical practise. This technology has revolutionised the laboratory cell biology and will provide much improved models of cell culture for drug discovery and development, as well as fundamental genetic basis studies of the disease. 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.

Trinucleotide repeat therapy

The mutation, called the trinucleotide repeat expansion disorders (TREDs), occurs when the number of triplets present in a mutated gene is greater than the number found in a normal gene [305]. Repeats of trinucleotides belong to simple sequence repeats, also known as short tandem repeats or microsatellites, and are common grounds in the human genomes and many other organisms [260]. RNA interference (RNAi) or antisense oligonucleotides (AON), utilizes repeat hairpin-specific small compounds and targeting repeats with mutant siRNAs acting as miRNAs use expanded repeat RNA as a target has been studied as experimental therapies for trinucleotide repeat expansion disorders [306].

RNAi reagents need a complementary sequence of ~20nt for successful silencing, which is only 7 repeats of CAG. Although normal CAG-bearing transcript alleles typically have 10–20 repeats, their mutant versions have 40–100 CAG repeats which means that transcripts from both alleles can be attacked by triplet duplexes of siRNA repeats [307]. RNA interference is currently being studied as a biological process as a potential therapy for Huntington's disease [308].

Different groups have employed various strategies to identify ligands that explicitly bind CUG and CAG repeat hairpins for the treatment of certain TREDs [309]. Screening a library of approximately 11 000 compounds yielded a few molecules which showed selectivity to bind to either short or extended CUG repeat hairpins [310]. These ligands were able to avoid *in vitro* interaction of the CUG repeat / muscleblind Like Splicing Regulator 1 (MBNL1) with a low constant of micromolar inhibition. In another research it has been shown that the small molecule inhibitors, pentamidine and neomycin B inhibit the interaction of short CUG repeat RNA with MBNL1 *in vitro* [311]. Multiple disorders of trinucleotides are not the only neurodegenerative condition that have withstood the production of successful therapies. Progress in curative therapy has also been sluggish for Alzheimer's, Parkinson's and other illnesses [270]. However, the production of therapies for repeat diseases with trinucleotides has one advantage: each disorder is caused by a defect in a single known gene [312]. Nucleic acid-based gene silencing has been used successfully in animals such as treatment of mice with virally expressed small hairpin (sh)RNAs, which decreases mutant human HTT mRNA or protein [312, 313].

Different therapeutic approaches were explored to achieve diseases with TNR. Some involve the use of RNAi or AONs to target and degrade transcripts that could trigger disease growth, (ii) antisense oligomers and small molecules to inhibit RNA – protein interactions, and (iii) modified antisense oligomers, siRNAs or miRNAs to prevent protein synthesis [306]. CCG repetitions in the RNA cause various neurological disorders and very little is understood about the treatment of these disorders and targeting the induction of the CCG with small molecules may be a beneficial approach to treating these conditions. Most of those small molecules are only successful repeats (CCG)exp for detection and may only be used for the aims of the treatment [314]. Expansion of GAA repeats on chromosome 9q13-q21.1 in the X25 frataxin gene causes Friedreich's ataxia (FRDA) disease [315]. Some of the therapeutic strategies for treating FRDA may be the reversal of the reduction of frataxin protein levels [316]. Additional small therapeutic molecules include the use of nicotinamide, dyclonine, and gene therapy to treat FRDA diseases [317-319].

Some other therapeutic approaches include the use of heat shock proteins (HSPs), which help the disease-causing polyQ proteins refold and solubilise [320, 321]. Therapeutic approaches for Spinal-bulbar muscular atrophy (SBMA) include either inhibiting the aggregation of causative androgen receptor (AR) protein or minimising the downstream pathological events, but a combination of both may be more successful as both therapies have their limitations recorded [322]. Small molecules such as epigallocatechin gallate (EGCG) have been reported to inhibit polyQ aggregation, and recent studies have shown that toxic RNA also participates in pathogenesis of the disease and that small molecular-based therapies may be suggested for targeting HD [323]. Patients with DRPLA suffer from choreoathetosis, autism, cerebellar ataxia, dementia, myoclonus and intellectual retardation [324, 325]. No cure for DRPLA is currently available, and only symptomatic treatments is provided to patients with DRPLA. Earlier attempts however suggest the use of ASOs to block mutant atrophin-1 expression [326]. Advances in the area of molecular pathogenesis of the condition and alternatives to the production of Myotonic Dystrophy therapies [327]. AONs shRNAs, and siRNAs were developed as the oculopharyngeal muscular dystrophy (OPMD) therapeutics. Some of the pharmacological inducing agents HSP70 such as 8- hydroxyquinolone and anti-inflammatory drugs such as ibuprofen and indomethacin have been documented to be successful in reducing polymutant alanine-mediated cytotoxicity of mutant alanine-exp PABPN1 expressing cells [328].

Expansion of the trinucleotide repeats is one of the main causes of neurodegenerative diseases. Nowadays have seen rapid progress in various cellular and animal model systems

developing experimental therapies for TREDs and tools for the study of disease processes and useful for the screening and evaluation of new therapeutic strategies. Conclusively, efforts by various research groups for a thorough understanding of RNA recognition and structure as well as commercial, clinical cooperation are crucial in developing small molecule based TRED therapies.

Conclusion

In summary, the intercellular communication of MSCs EVs carry a specific cargo of miRNAs secreted into the nervous system. Their role is to maintain physiological function and providing neuroprotection. In addition, MSCs EVs help promote tissue repair and regeneration. While deregulation of this intercellular communication may promote the progression of a number of 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. At the same time, providing a potential early diagnostic strategy. There are a few clinical trial studies 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.

Figure legends

Figure 1. Overview of miRNA synthesis and extracellular vesicle miRNA transfer to 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 then 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.

Figure 2. EVs contents derived from normal versus ND affected brain tissue. Normal brain secretes EVs that carry cargos, including lipids, nucleic acids, and proteins, while neurodegenerative EVs carry specific proteins that are associated with the disease. Alzheimer's disease derived-EVs carry 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 and 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.

Table 1. Alzheimer's Disease Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated. The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease.15-LOX- Arachidonate 15-Lipoxygenase; ApoE- Apolipoprotein E; APP- Amyloid Precursor Protein; Atg4d- Autophagy Related 4D Cysteine Peptidase; BACE1- Beta-Secretase 1; BECN1- Beclin1; BTBD3- BTB Domain Containing 3; CDKN2- Cyclin Dependent Kinase Inhibitor 2A; CFH- Complement Factor H; CSF- Cerebrospinal Fluid; ECF- Extracellular Fluid; GMEB2- Glucocorticoid Modulatory Element Binding Protein 2; IDH2- Isocitrate Dehydrogenase (NADP(+)) 2; p250GAP- p250 GTPase Activating Protein ; PTBP2- Polypyrimidine Tract Binding Protein 2; PTPN1- Protein Tyrosine Phosphatase Non-Receptor

Type 1; SIRT1- Sirtuin 1; SNAP25- Synaptosome Associated Protein 25; SPT- Suppressor of Ty; STX1A- Syntaxin 1A; SYN-2- Synapsin II; SYNJ1- Synaptojanin 1; SYNPR- Synaptoporin; SYT1- Synaptotagmin 1; TGFBI- Transforming Growth Factor Beta Induced; TLR- Toll Like Receptor; TRIM2- Tripartite Motif Containing 2; UNC13B- Unc-13 HomologB

Table 2. Parkinson's Disease- Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated (e.g. cultured neuronal cells). The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease. ATP5G3- ATP Synthase Membrane Subunit C Locus 3; Bax- BCL2 Associated X, Apoptosis Regulator; DRAM- DNA damage regulated autophagy modulator 1; GLUT3- Glucose Transporter Type 3, Brain; HSC70- Heat Shock Protein Family A (Hsp70) Member 8; HSP70- Heat Shock Protein Family A (Hsp70) Member 4; KEAP1- Kelch Like ECH Associated Protein 1; LAMP2a- Lysosomal Associated Membrane Protein 2; LRRK2- Leucine Rich Repeat Kinase 2; MTFMT- Mitochondrial Methionyl-TRNA Formyltransferase; NFκB- Nuclear Factor Kappa B Subunit 1; NLRP3- NLR Family Pyrin Domain Containing 3; PARK2- Parkinson Disease (Autosomal Recessive, Juvenile) 2, Parkin; PARK7- Parkinson Disease (Autosomal Recessive, Early Onset) 7; PARK8 - Parkinson Disease (Autosomal Dominant) 8; RELA- v-rel reticuloendotheliosis viral oncogene homolog A (avian); SIAH1- Seven In Absentia Homolog 1; SNCA- Synuclein Alpha; TFEB- Transcription Factor EB; TNF-α- Tumor Necrosis Factor-Alpha ; VDAC1- Voltage Dependent Anion Channel 1; XIRP2- Xin Actin Binding Repeat Containing 2; ZNF440- Zinc Finger Protein 440; α-SYN- Synuclein Alpha

Table 3 Prion Disease Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated (e.g. mouse brain). The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease. CFH- Complement Factor H; DCX- Doublecortin; E2F1- E2F Transcription Factor 1; ERK1 - Extracellular Signal-Regulated Kinase1; IL-8- Interleukin 8 ; IRAK-1- Interleukin 1 Receptor Associated Kinase 1; MAPK1-Mitogen-Activated Protein Kinase 1; ERK2- Extracellular Signal-Regulated Kinase 2; MAPK3- Mitogen-Activated Protein Kinase 3; PLCE1- Phospholipase C Epsilon 1; ROCK2- Rho Associated Coiled-Coil Containing Protein Kinase 2; TREM2- Triggering Receptor Expressed On Myeloid Cells 2;

ULK1- Unc-51 Like Autophagy Activating Kinase 1; VEGF- Vascular Endothelial Growth Factor A

Table 4. Huntingtons Disease Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated (e.g. STHdhQ111/HdhQ111 cells; monkey brain). The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease. Ago2- Argonaute RISC Catalytic Component 2; BDNF- Brain Derived Neurotrophic Factor; CREB1 - CAMP Responsive Element Binding Protein 1; Foxg1- Forkhead Box G1; HIP-1- Huntingtin Interacting Protein 1; HDAC4- Histone Deacetylase 4; HTT- Huntingtin; MeCP2- Methyl; CpG Binding Protein 2; p250GAP- p250 GTPase Activating Protein; PGC1- PPARG Coactivator 1 Alpha ; PTB1- Polypyrimidine tract-binding protein 1; REST- RE1 Silencing Transcription Factor; Rgs2- Regulator Of G Protein Signaling 2; Rgs8- Regulator Of G Protein Signaling 8; SOX9- SRY-Box Transcription Factor 9; SP-1- Sp1 Transcription Factor; TBP- TATA-Box Binding Protein; VEGF-A- Vascular Endothelial Growth Factor A

Table 5. Amyotrophic lateral sclerosis-Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated. The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease. 43TARDBP- TAR DNA-Binding Protein 43; ABCG1- ATP Binding Cassette Subfamily G Member 1; ARHGDIA- Rho GDP Dissociation Inhibitor Alpha; BAX- BCL2 Associated X, Apoptosis Regulator; BBC3- BCL2 Binding Component 3; BSG- Basigin (Ok Blood Group); C9orf72- Chromosome 9 Open Reading Frame 72; CD151- CD151 Molecule (Raph Blood Group); CDKN2D- Cyclin Dependent Kinase Inhibitor 2D; CTDSP1- Carboxy-Terminal Domain RNA Polymerase II Polypeptide A Small Phosphatase 1; FLOT1- Flotillin 1; FUS- Fused In Sarcoma; GRB10- Growth Factor Receptor Bound Protein 10; HAX1- HCLS1 Associated Protein X-1; HDGF- Heparin Binding Growth Factor; HMGA1- High Mobility Group AT-Hook 1; IER2- Immediate Early Response 2; ITGA5- Integrin Subunit Alpha 5; LGALS3- Galectin 3; MAPK3- Mitogen-Activated Protein Kinase 3; MIEN1- Migration And Invasion Enhancer 1; MT2A- Metallothionein 2A; MT-CO2- Mitochondrially Encoded Cytochrome C Oxidase II; MYL9-Myosin Light Chain 9; MYO1F- Myosin IF ; NFKBIB- NF-Kappa-B Inhibitor Beta; OTUB1- OTU Deubiquitinase, Ubiquitin Aldehyde Binding 1; PFN1- Profilin 1; PHB- Prohibitin; PINK1- PTEN Induced Kinase 1; PKM- Pyruvate Kinase M1/2; PRKCD- Protein Kinase C Delta; PTMS- Parathymosin; PTPA-

Protein Phosphatase 2 Phosphatase Activator; PTTG1- Pituitary Tumor-Transforming Gene 1 Protein; RAB40C- Ras-Related Protein Rab-40C; RHOC- Ras Homolog Family Member C; SMARCD3- SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily D, Member 3; SNAI3- Snail Family Transcriptional Repressor 3; SOD1- Superoxide Dismutase 1; TACC3- Transforming Acidic Coiled-Coil Containing Protein 3; UCP2- uncoupling Protein 2; VIM- Vimentin; ZYX- Zyxin

Table 6. Multiple Sclerosis Micro RNAs and possible targets All miRNA–target relationships shown here are in humans unless indicated (e.g. Th17 cell line; EAE mice). The miRNAs and genes mentioned in the table has shown direct or indirect relationship in the pathogenesis and progression of the disease. ABCA1- ATP Binding Cassette Subfamily A Member 1; ADD2- Adducin 2; AID- activation induced deaminase; AKR1C1- Aldo-Keto Reductase Family 1 Member C1; AKR1C2- Aldo-Keto Reductase Family 1 Member C2; BACH1- BTB Domain And CNC Homolog 1; BACH2- BTB Domain And CNC Homolog 2; BCL2- BCL2 Apoptosis Regulator; CEBPB- CCAAT Enhancer Binding Protein Beta; CFH- Complement Factor H; c-MAF- C-Maf Inducing Protein; CSFR- Colony Stimulating Factor 1 Receptor ; DIP2A- Disco Interacting Protein 2 Homolog A; Dnaja2- DnaJ Heat Shock Protein Family (Hsp40) Member A2; Dnajb1- DnaJ Heat Shock Protein Family (Hsp40) Member B1; E2F2- E2F Transcription Factor 2; FADD- Fas Associated Via Death Domain; FOXO1- Forkhead Box O1; GPX3- Glutathione Peroxidase 3; HSP40- Heat Shock 40 KDa Protein; IKZF1- Ikaros family zinc finger 4; IL-17- Interleukin 17A; Il23r- Interleukin 23 Receptor; IRAK-1- Interleukin 1 Receptor Associated Kinase 1; IRAK-2- Interleukin 1 Receptor Associated Kinase 2; JARID2- Jumonji And AT-Rich Interaction Domain Containing 2; MMP-9- Matrix Metallopeptidase 9; Myb- MYB Proto-Oncogene, Transcription Factor; Mef2- Myocyte enhancer factor-2; NKRF- NFKB Repressing Factor; PGC-1α- PPARG Coactivator 1 Alpha; PIAS3- Protein Inhibitor Of Activated STAT 3; PTEN - Phosphatase And Tensin Homolog; Ripk1- Receptor Interacting Serine/Threonine Kinase 1; SOCS1- Suppressor Of Cytokine Signaling 1; tab2- TGF-Beta Activated Kinase 1 (MAP3K7) Binding Protein 2; Tbx21- T-Box Transcription Factor 21; TMED7- Transmembrane P24 Trafficking Protein 7; TRAF6- TNF Receptor Associated Factor 6

Table 7 – Characteristics of miRNAs binding sites in CDS mRNA genes with nucleotide repeats

Table 8 Current stem cell development

References:

1. Wang, Y., et al., *Stem cell therapies in age-related neurodegenerative diseases and stroke.* Ageing Res Rev, 2017. **34**: p. 39-50.
2. Lee, R.H., et al., *Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6.* Cell Stem Cell, 2009. **5**(1): p. 54-63.
3. Iso, Y., et al., *Multipotent human stromal cells improve cardiac function after myocardial infarction in mice without long-term engraftment.* Biochem Biophys Res Commun, 2007. **354**(3): p. 700-6.
4. Gao, J., et al., *The dynamic in vivo distribution of bone marrow-derived mesenchymal stem cells after infusion.* Cells Tissues Organs, 2001. **169**(1): p. 12-20.
5. Bruno, S., et al., *Role of extracellular vesicles in stem cell biology.* Am J Physiol Cell Physiol, 2019. **317**(2): p. C303-c313.
6. Lai, R.C., et al., *Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury.* Stem Cell Res, 2010. **4**(3): p. 214-22.
7. Bruno, S., et al., *Mesenchymal stem cell-derived microvesicles protect against acute tubular injury.* J Am Soc Nephrol, 2009. **20**(5): p. 1053-67.
8. van Niel, G., G. D'Angelo, and G. Raposo, *Shedding light on the cell biology of extracellular vesicles.* Nat Rev Mol Cell Biol, 2018. **19**(4): p. 213-228.
9. Skog, J., et al., *Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers.* Nat Cell Biol, 2008. **10**(12): p. 1470-6.
10. Lai, C.P., et al., *Visualization and tracking of tumour extracellular vesicle delivery and RNA translation using multiplexed reporters.* Nat Commun, 2015. **6**: p. 7029.
11. Ratajczak, J., et al., *Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery.* Leukemia, 2006. **20**(5): p. 847-56.
12. Valadi, H., et al., *Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells.* Nat Cell Biol, 2007. **9**(6): p. 654-9.
13. Zhuang, X., et al., *Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain.* Mol Ther, 2011. **19**(10): p. 1769-79.
14. Uccelli, A., L. Moretta, and V. Pistoia, *Mesenchymal stem cells in health and disease.* Nat Rev Immunol, 2008. **8**(9): p. 726-36.
15. Romanov, Y.A., V.A. Svintsitskaya, and V.N. Smirnov, *Searching for alternative sources of postnatal human mesenchymal stem cells: candidate MSC-like cells from umbilical cord.* Stem Cells, 2003. **21**(1): p. 105-10.
16. Zuk, P.A., et al., *Human adipose tissue is a source of multipotent stem cells.* Mol Biol Cell, 2002. **13**(12): p. 4279-95.
17. In 't Anker, P.S., et al., *Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation.* Blood, 2003. **102**(4): p. 1548-9.
18. Fukuchi, Y., et al., *Human placenta-derived cells have mesenchymal stem/progenitor cell potential.* Stem Cells, 2004. **22**(5): p. 649-58.
19. Boyle, A.J., I.K. McNiece, and J.M. Hare, *Mesenchymal stem cell therapy for cardiac repair.* Methods Mol Biol, 2010. **660**: p. 65-84.
20. Bhandari, D.R., et al., *The simplest method for in vitro beta-cell production from human adult stem cells.* Differentiation, 2011. **82**(3): p. 144-52.
21. Banas, A., et al., *Adipose tissue-derived mesenchymal stem cells as a source of human hepatocytes.* Hepatology, 2007. **46**(1): p. 219-28.

22. Pournasr, B., et al., *In vitro differentiation of human bone marrow mesenchymal stem cells into hepatocyte-like cells.* Arch Iran Med, 2011. **14**(4): p. 244-9.
23. Yin, L., et al., *Adipose tissue-derived mesenchymal stem cells differentiated into hepatocyte-like cells in vivo and in vitro.* Mol Med Rep, 2015. **11**(3): p. 1722-32.
24. Ferrari, G., et al., *Muscle regeneration by bone marrow-derived myogenic progenitors.* Science, 1998. **279**(5356): p. 1528-30.
25. Planat-Benard, V., et al., *Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells.* Circ Res, 2004. **94**(2): p. 223-9.
26. Rodriguez, L.V., et al., *Clonogenic multipotent stem cells in human adipose tissue differentiate into functional smooth muscle cells.* Proc Natl Acad Sci U S A, 2006. **103**(32): p. 12167-72.
27. Sanchez-Ramos, J., et al., *Adult bone marrow stromal cells differentiate into neural cells in vitro.* Exp Neurol, 2000. **164**(2): p. 247-56.
28. Wosnitza, M., et al., *Plasticity of human adipose stem cells to perform adipogenic and endothelial differentiation.* Differentiation, 2007. **75**(1): p. 12-23.
29. Majumdar, M.K., et al., *Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages.* J Hematother Stem Cell Res, 2000. **9**(6): p. 841-8.
30. Bifari, F., et al., *Immune Modulation by Mesenchymal Stem Cells.* Transfus Med Hemother, 2008. **35**(3): p. 194-204.
31. Forbes, G.M., et al., *A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy.* Clin Gastroenterol Hepatol, 2014. **12**(1): p. 64-71.
32. Gonzalez, M.A., et al., *Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses.* Gastroenterology, 2009. **136**(3): p. 978-89.
33. Le Blanc, K., et al., *HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells.* Exp Hematol, 2003. **31**(10): p. 890-6.
34. Aggarwal, S. and M.F. Pittenger, *Human mesenchymal stem cells modulate allogeneic immune cell responses.* Blood, 2005. **105**(4): p. 1815-22.
35. Corcione, A., et al., *Human mesenchymal stem cells modulate B-cell functions.* Blood, 2006. **107**(1): p. 367-72.
36. Jiang, X.X., et al., *Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells.* Blood, 2005. **105**(10): p. 4120-6.
37. Nauta, A.J. and W.E. Fibbe, *Immunomodulatory properties of mesenchymal stromal cells.* Blood, 2007. **110**(10): p. 3499-506.
38. Shi, M., Z.W. Liu, and F.S. Wang, *Immunomodulatory properties and therapeutic application of mesenchymal stem cells.* Clin Exp Immunol, 2011. **164**(1): p. 1-8.
39. Chapel, A., et al., *Mesenchymal stem cells home to injured tissues when co-infused with hematopoietic cells to treat a radiation-induced multi-organ failure syndrome.* J Gene Med, 2003. **5**(12): p. 1028-38.
40. Fong, E.L., C.K. Chan, and S.B. Goodman, *Stem cell homing in musculoskeletal injury.* Biomaterials, 2011. **32**(2): p. 395-409.
41. Mouiseddine, M., et al., *Human mesenchymal stem cells home specifically to radiation-injured tissues in a non-obese diabetes/severe combined immunodeficiency mouse model.* Br J Radiol, 2007. **80 Spec No 1**: p. S49-55.
42. Kidd, S., et al., *Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using in vivo bioluminescent imaging.* Stem Cells, 2009. **27**(10): p. 2614-23.

43. Galland, S. and I. Stamenkovic, *Mesenchymal stromal cells in cancer: a review of their immunomodulatory functions and dual effects on tumor progression.* J Pathol, 2020. **250**(5): p. 555-572.
44. Thery, C., et al., *Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines.* J Extracell Vesicles, 2018. **7**(1): p. 1535750.
45. Latifkar, A., et al., *New insights into extracellular vesicle biogenesis and function.* J Cell Sci, 2019. **132**(13).
46. Gezsi, A., et al., *Systems biology approaches to investigating the roles of extracellular vesicles in human diseases.* Exp Mol Med, 2019. **51**(3): p. 1-11.
47. Tang, T.T., et al., *Extracellular Vesicles: Opportunities and Challenges for the Treatment of Renal Diseases.* Front Physiol, 2019. **10**: p. 226.
48. Kishore, R. and M. Khan, *More Than Tiny Sacks: Stem Cell Exosomes as Cell-Free Modality for Cardiac Repair.* Circ Res, 2016. **118**(2): p. 330-43.
49. Bebelman, M.P., et al., *Biogenesis and function of extracellular vesicles in cancer.* Pharmacol Ther, 2018. **188**: p. 1-11.
50. Kirchner, B., et al., *Postprandial transfer of colostral extracellular vesicles and their protein and miRNA cargo in neonatal calves.* PLoS One, 2020. **15**(2): p. e0229606.
51. Cufaro, M.C., et al., *Extracellular Vesicles and Their Potential Use in Monitoring Cancer Progression and Therapy: The Contribution of Proteomics.* J Oncol, 2019. **2019**: p. 1639854.
52. Tricarico, C., J. Clancy, and C. D'Souza-Schorey, *Biology and biogenesis of shed microvesicles.* Small GTPases, 2017. **8**(4): p. 220-232.
53. Kalra, H., et al., *Vesiclepedia: a compendium for extracellular vesicles with continuous community annotation.* PLoS Biol, 2012. **10**(12): p. e1001450.
54. S.;, E.-A., et al., *Extracellular vesicles: biology and emerging therapeutic opportunities.* Nat Rev Drug Discov, 2013. **12**(5): p. 347-57.
55. Borges, F.T., L.A. Reis, and N. Schor, *Extracellular vesicles: structure, function, and potential clinical uses in renal diseases.* Braz J Med Biol Res, 2013. **46**(10): p. 824-30.
56. Bayraktar, R., K. Van Roosbroeck, and G.A. Calin, *Cell-to-cell communication: microRNAs as hormones.* Mol Oncol, 2017. **11**(12): p. 1673-1686.
57. Ihara, T., et al., *The process of ultrastructural changes from nuclei to apoptotic body.* Virchows Arch, 1998. **433**(5): p. 443-7.
58. Doyle, L.M. and M.Z. Wang, *Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis.* Cells, 2019. **8**(7).
59. Mettinger, K.L.R., P.; Kumar, V., *Exosomes, Stem Cells and MicroRNA. Aging, Cancer and Age Related Disorders* Advances in Experimental Medicine and Biology. 2018: Springer.
60. Temoche-Diaz, M.M., et al., *Distinct mechanisms of microRNA sorting into cancer cell-derived extracellular vesicle subtypes.* Elife, 2019. **8**.
61. Pfeifer, P., N. Werner, and F. Jansen, *Role and Function of MicroRNAs in Extracellular Vesicles in Cardiovascular Biology.* Biomed Res Int, 2015. **2015**: p. 161393.
62. Ceafalan, L.C.I., O.C.; Marta, D.S.; Constantin, A.; Alexandru, N.; Nemecz, M.; Tanko, G.; Filippi, A.; Magda, S.L.; Bojin, F.; Paunescu, V.; Vinereanu, D.; Georgescu, A.; Gherghiceanu, M., *Part Two: Extracellular Vesicles as a Risk Factor*

in Neurodegenerative Diseases. Extracellular Vesicles and Their Importance in Human Health. 2019: IntechOpen.
63. Ciregia, F., A. Urbani, and G. Palmisano, *Extracellular Vesicles in Brain Tumors and Neurodegenerative Diseases.* Front Mol Neurosci, 2017. **10**: p. 276.
64. Caruso Bavisotto, C., et al., *Extracellular Vesicle-Mediated Cell(-)Cell Communication in the Nervous System: Focus on Neurological Diseases.* Int J Mol Sci, 2019. **20**(2).
65. Peters, A. and A. Fairen, *Smooth and sparsely-spined stellate cells in the visual cortex of the rat: a study using a combined Golgi-electron microscopic technique.* J Comp Neurol, 1978. **181**(1): p. 129-71.
66. Isola, A.L. and S. Chen, *Exosomes: The Messengers of Health and Disease.* Curr Neuropharmacol, 2017. **15**(1): p. 157-165.
67. Arenaccio, C. and M. Federico, *The Multifaceted Functions of Exosomes in Health and Disease: An Overview.* Adv Exp Med Biol, 2017. **998**: p. 3-19.
68. Lu, K.-C., Y. Zhang, and E. Song, *Extracellular RNA: mechanisms of it's transporting into target cells.* ExRNA, 2019. **1**(1): p. 22.
69. Lund-Katz, S. and M.C. Phillips, *High density lipoprotein structure-function and role in reverse cholesterol transport.* Subcell Biochem, 2010. **51**: p. 183-227.
70. Vickers, K.C., et al., *MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins.* Nat Cell Biol, 2011. **13**(4): p. 423-33.
71. Witwer, K.W. and C. Thery, *Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature.* J Extracell Vesicles, 2019. **8**(1): p. 1648167.
72. Chiang, C.Y. and C. Chen, *Toward characterizing extracellular vesicles at a single-particle level.* J Biomed Sci, 2019. **26**(1): p. 9.
73. Liu, W., et al., *Role of Exosomes in Central Nervous System Diseases.* Front Mol Neurosci, 2019. **12**: p. 240.
74. Blackburn, D., et al., *Astrocyte function and role in motor neuron disease: a future therapeutic target?* Glia, 2009. **57**(12): p. 1251-64.
75. Sidoryk-Wegrzynowicz, M., et al., *Role of astrocytes in brain function and disease.* Toxicol Pathol, 2011. **39**(1): p. 115-23.
76. Sofroniew, M.V., *Astrocyte barriers to neurotoxic inflammation.* Nat Rev Neurosci, 2015. **16**(5): p. 249-63.
77. Agnati, L.F., et al., *Information handling by the brain: proposal of a new "paradigm" involving the roamer type of volume transmission and the tunneling nanotube type of wiring transmission.* J Neural Transm (Vienna), 2014. **121**(12): p. 1431-49.
78. Guescini, M., et al., *Astrocytes and Glioblastoma cells release exosomes carrying mtDNA.* J Neural Transm (Vienna), 2010. **117**(1): p. 1-4.
79. Pascua-Maestro, R., et al., *Extracellular Vesicles Secreted by Astroglial Cells Transport Apolipoprotein D to Neurons and Mediate Neuronal Survival Upon Oxidative Stress.* Front Cell Neurosci, 2018. **12**: p. 526.
80. Taylor, A.R., et al., *Regulation of heat shock protein 70 release in astrocytes: role of signaling kinases.* Dev Neurobiol, 2007. **67**(13): p. 1815-29.
81. Wang, G., et al., *Astrocytes secrete exosomes enriched with proapoptotic ceramide and prostate apoptosis response 4 (PAR-4): potential mechanism of apoptosis induction in Alzheimer disease (AD).* J Biol Chem, 2012. **287**(25): p. 21384-95.
82. Willis, C.M., et al., *A Refined Bead-Free Method to Identify Astrocytic Exosomes in Primary Glial Cultures and Blood Plasma.* Front Neurosci, 2017. **11**: p. 335.
83. Venturini, A., et al., *Exosomes From Astrocyte Processes: Signaling to Neurons.* Front Pharmacol, 2019. **10**: p. 1452.

84. Gosselin, R.D., P. Meylan, and I. Decosterd, *Extracellular microvesicles from astrocytes contain functional glutamate transporters: regulation by protein kinase C and cell activation.* Front Cell Neurosci, 2013. **7**: p. 251.
85. Guitart, K., et al., *Improvement of neuronal cell survival by astrocyte-derived exosomes under hypoxic and ischemic conditions depends on prion protein.* Glia, 2016. **64**(6): p. 896-910.
86. Kuhn, S., et al., *Oligodendrocytes in Development, Myelin Generation and Beyond.* Cells, 2019. **8**(11).
87. Domingues, H.S., et al., *Corrigendum: Oligodendrocyte, Astrocyte and Microglia Crosstalk in Myelin Development, Damage, and Repair.* Front Cell Dev Biol, 2016. **4**: p. 79.
88. Fruhbeis, C., et al., *Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication.* PLoS Biol, 2013. **11**(7): p. e1001604.
89. Frohlich, D., et al., *Multifaceted effects of oligodendroglial exosomes on neurons: impact on neuronal firing rate, signal transduction and gene regulation.* Philos Trans R Soc Lond B Biol Sci, 2014. **369**(1652).
90. Frühbeis, C., et al., *Oligodendrocyte-derived exosomes promote axonal transport and axonal long-term maintenance.* bioRxiv, 2019: p. 2019.12.20.884171.
91. Delpech, J.C., et al., *Neuroimmune Crosstalk through Extracellular Vesicles in Health and Disease.* Trends Neurosci, 2019. **42**(5): p. 361-372.
92. Yin, J., et al., *The Role of Microglia and Macrophages in CNS Homeostasis, Autoimmunity, and Cancer.* J Immunol Res, 2017. **2017**: p. 5150678.
93. Ueno, M., et al., *Layer V cortical neurons require microglial support for survival during postnatal development.* Nat Neurosci, 2013. **16**(5): p. 543-51.
94. Glebov, K., et al., *Serotonin stimulates secretion of exosomes from microglia cells.* Glia, 2015. **63**(4): p. 626-34.
95. Potolicchio, I., et al., *Proteomic analysis of microglia-derived exosomes: metabolic role of the aminopeptidase CD13 in neuropeptide catabolism.* J Immunol, 2005. **175**(4): p. 2237-43.
96. Drago, F., et al., *ATP Modifies the Proteome of Extracellular Vesicles Released by Microglia and Influences Their Action on Astrocytes.* Front Pharmacol, 2017. **8**: p. 910.
97. Faure, J., et al., *Exosomes are released by cultured cortical neurones.* Mol Cell Neurosci, 2006. **31**(4): p. 642-8.
98. Lachenal, G., et al., *Release of exosomes from differentiated neurons and its regulation by synaptic glutamatergic activity.* Mol Cell Neurosci, 2011. **46**(2): p. 409-18.
99. Sharma, P., et al., *Exosomes regulate neurogenesis and circuit assembly.* Proc Natl Acad Sci U S A, 2019. **116**(32): p. 16086-16094.
100. Bahrini, I., et al., *Neuronal exosomes facilitate synaptic pruning by up-regulating complement factors in microglia.* Sci Rep, 2015. **5**: p. 7989.
101. Lee, S., S. Mankhong, and J.H. Kang, *Extracellular Vesicle as a Source of Alzheimer's Biomarkers: Opportunities and Challenges.* Int J Mol Sci, 2019. **20**(7).
102. Corder, E.H., et al., *Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families.* Science, 1993. **261**(5123): p. 921-3.
103. Farrer, L.A., et al., *Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium.* Jama, 1997. **278**(16): p. 1349-56.
104. Rajendran, L., et al., *Alzheimer's disease beta-amyloid peptides are released in association with exosomes.* Proc Natl Acad Sci U S A, 2006. **103**(30): p. 11172-7.

105. Sharples, R.A., et al., *Inhibition of gamma-secretase causes increased secretion of amyloid precursor protein C-terminal fragments in association with exosomes.* Faseb j, 2008. **22**(5): p. 1469-78.
106. Asai, H., et al., *Depletion of microglia and inhibition of exosome synthesis halt tau propagation.* Nat Neurosci, 2015. **18**(11): p. 1584-93.
107. Dinkins, M.B., et al., *Exosome reduction in vivo is associated with lower amyloid plaque load in the 5XFAD mouse model of Alzheimer's disease.* Neurobiol Aging, 2014. **35**(8): p. 1792-800.
108. Serrano-Pozo, A., et al., *Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease.* Am J Pathol, 2011. **179**(3): p. 1373-84.
109. Crotti, A., et al., *BIN1 favors the spreading of Tau via extracellular vesicles.* Sci Rep, 2019. **9**(1): p. 9477.
110. Nelson, P.T. and W.X. Wang, *MiR-107 is reduced in Alzheimer's disease brain neocortex: validation study.* J Alzheimers Dis, 2010. **21**(1): p. 75-9.
111. Zhu, H.C., et al., *MicroRNA-195 downregulates Alzheimer's disease amyloid-β production by targeting BACE1.* Brain Res Bull, 2012. **88**(6): p. 596-601.
112. Kim, J., et al., *MiR-106b impairs cholesterol efflux and increases Aβ levels by repressing ABCA1 expression.* Exp Neurol, 2012. **235**(2): p. 476-83.
113. Ben Halima, S., G. Siegel, and L. Rajendran, *miR-186 in Alzheimer's disease: a big hope for a small RNA?* J Neurochem, 2016. **137**(3): p. 308-11.
114. Patel, N., et al., *MicroRNAs can regulate human APP levels.* Mol Neurodegener, 2008. **3**: p. 10.
115. Yang, L.B., et al., *Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease.* Nat Med, 2003. **9**(1): p. 3-4.
116. Tiwari, S., et al., *Alzheimer's disease: pathogenesis, diagnostics, and therapeutics.* Int J Nanomedicine, 2019. **14**: p. 5541-5554.
117. Vickrey, B.G., et al., *The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial.* Ann Intern Med, 2006. **145**(10): p. 713-26.
118. Voisin, T. and B. Vellas, *Diagnosis and treatment of patients with severe Alzheimer's disease.* Drugs Aging, 2009. **26**(2): p. 135-44.
119. Emamzadeh, F.N. and A. Surguchov, *Parkinson's Disease: Biomarkers, Treatment, and Risk Factors.* Front Neurosci, 2018. **12**: p. 612.
120. Zafar, S. and S.S. Yaddanapudi, *Parkinson Disease.* 2020: StatPearls.
121. Poewe, W., et al., *Parkinson disease.* Nat Rev Dis Primers, 2017. **3**: p. 17013.
122. El-Agnaf, O.M., et al., *Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma.* Faseb j, 2003. **17**(13): p. 1945-7.
123. Emmanouilidou, E., et al., *Cell-produced alpha-synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival.* J Neurosci, 2010. **30**(20): p. 6838-51.
124. Alvarez-Erviti, L., et al., *Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission.* Neurobiol Dis, 2011. **42**(3): p. 360-7.
125. Danzer, K.M., et al., *Exosomal cell-to-cell transmission of alpha synuclein oligomers.* Mol Neurodegener, 2012. **7**: p. 42.
126. Cao, Z., et al., *alpha-Synuclein in salivary extracellular vesicles as a potential biomarker of Parkinson's disease.* Neurosci Lett, 2019. **696**: p. 114-120.
127. Chang, C., et al., *Exosomes of BV-2 cells induced by alpha-synuclein: important mediator of neurodegeneration in PD.* Neurosci Lett, 2013. **548**: p. 190-5.

128. Cooper, J.M., et al., *Systemic exosomal siRNA delivery reduced alpha-synuclein aggregates in brains of transgenic mice.* Mov Disord, 2014. **29**(12): p. 1476-85.
129. Haney, M.J., et al., *Exosomes as drug delivery vehicles for Parkinson's disease therapy.* J Control Release, 2015. **207**: p. 18-30.
130. Etheridge, A., et al., *Extracellular microRNA: a new source of biomarkers.* Mutat Res, 2011. **717**(1-2): p. 85-90.
131. Kamal, M.A., G. Mushtaq, and N.H. Greig, *Current Update on Synopsis of miRNA Dysregulation in Neurological Disorders.* CNS Neurol Disord Drug Targets, 2015. **14**(4): p. 492-501.
132. Palanichamy, J.K. and D.S. Rao, *miRNA dysregulation in cancer: towards a mechanistic understanding.* Front Genet, 2014. **5**: p. 54.
133. Goh, S.Y., et al., *Role of MicroRNAs in Parkinson's Disease.* Int J Mol Sci, 2019. **20**(22).
134. Miñones-Moyano, E., et al., *MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR-34b/c which modulate mitochondrial function.* Hum Mol Genet, 2011. **20**(15): p. 3067-78.
135. Cookson, M.R., *Parkinsonism due to mutations in PINK1, parkin, and DJ-1 and oxidative stress and mitochondrial pathways.* Cold Spring Harb Perspect Med, 2012. **2**(9): p. a009415.
136. Shimura, H., et al., *Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase.* Nat Genet, 2000. **25**(3): p. 302-5.
137. Illarioshkin, S.N., et al., *Mutation analysis of the parkin gene in Russian families with autosomal recessive juvenile parkinsonism.* Mov Disord, 2003. **18**(8): p. 914-9.
138. Imran, M. and S. Mahmood, *An overview of human prion diseases.* Virol J, 2011. **8**: p. 559.
139. Avni, A., et al., *Intrinsically disordered proteins in the formation of functional amyloids from bacteria to humans.* Prog Mol Biol Transl Sci, 2019. **166**: p. 109-143.
140. Creutzfeldt, H.G., *On a particular focal disease of the central nervous system (preliminary communication), 1920.* Alzheimer Dis Assoc Disord, 1989. **3**(1-2): p. 3-25.
141. Duckett, S. and J. Stern, *Origins of the Creutzfeldt and Jakob concept.* J Hist Neurosci, 1999. **8**(1): p. 21-34.
142. Kübler, E., B. Oesch, and A.J. Raeber, *Diagnosis of prion diseases.* Br Med Bull, 2003. **66**: p. 267-79.
143. Puckett, C., et al., *Genomic structure of the human prion protein gene.* Am J Hum Genet, 1991. **49**(2): p. 320-9.
144. Mackenzie, G. and R. Will, *Creutzfeldt-Jakob disease: recent developments.* F1000Res, 2017. **6**: p. 2053.
145. Chen, C. and X.P. Dong, *Epidemiological characteristics of human prion diseases.* Infect Dis Poverty, 2016. **5**(1): p. 47.
146. Mead, S., et al., *Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics.* Science, 2003. **300**(5619): p. 640-3.
147. Geschwind, M.D., *Prion Diseases.* Continuum (Minneap Minn), 2015. **21**(6 Neuroinfectious Disease): p. 1612-38.
148. Roos, R., D.C. Gajdusek, and C.J. Gibbs, Jr., *The clinical characteristics of transmissible Creutzfeldt-Jakob disease.* Brain, 1973. **96**(1): p. 1-20.
149. Masters, C.L., D.C. Gajdusek, and C.J. Gibbs, Jr., *Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Straussler syndrome with an analysis of the various forms of amyloid plaque deposition in the virus-induced spongiform encephalopathies.* Brain, 1981. **104**(3): p. 559-88.

150. Colby, D.W. and S.B. Prusiner, *Prions.* Cold Spring Harb Perspect Biol, 2011. **3**(1): p. a006833.
151. Prusiner, S.B., *Prions.* Proc Natl Acad Sci U S A, 1998. **95**(23): p. 13363-83.
152. Mastrianni, J.A., *The genetics of prion diseases.* Genet Med, 2010. **12**(4): p. 187-95.
153. Noble, G.P., et al., *Requirements for mutant and wild-type prion protein misfolding in vitro.* Biochemistry, 2015. **54**(5): p. 1180-7.
154. Kovács, G.G., et al., *Genetic prion disease: the EUROCJD experience.* Hum Genet, 2005. **118**(2): p. 166-74.
155. Erginel-Unaltuna, N., et al., *Distribution of the M129V polymorphism of the prion protein gene in a Turkish population suggests a high risk for Creutzfeldt-Jakob disease.* Eur J Hum Genet, 2001. **9**(12): p. 965-8.
156. Kaski, D., et al., *Variant CJD in an individual heterozygous for PRNP codon 129.* Lancet, 2009. **374**(9707): p. 2128.
157. Gajdusek, D.C., C.J. Gibbs, and M. Alpers, *Experimental transmission of a Kuru-like syndrome to chimpanzees.* Nature, 1966. **209**(5025): p. 794-6.
158. Lindenbaum, L., *An annotated history of kuru.* Medicine Anthropology Theory 2. Vol. 1. 2015. 95-126.
159. Radford, A.J., *Singsings, sutures & sorcery : a 50 year experience in Papua New Guinea : a dokta at large in the land of the unexpected.* 2012: Preston, Vic. : Mosaic Press, 2012.
160. Liberski, P.P., et al., *Kuru, the First Human Prion Disease.* Viruses, 2019. **11**(3).
161. Wadsworth, J.D., et al., *Kuru prions and sporadic Creutzfeldt-Jakob disease prions have equivalent transmission properties in transgenic and wild-type mice.* Proc Natl Acad Sci U S A, 2008. **105**(10): p. 3885-90.
162. Kosik, K.S., *The neuronal microRNA system.* Nat Rev Neurosci, 2006. **7**(12): p. 911-20.
163. Llorens, F., et al., *Regional and subtype-dependent miRNA signatures in sporadic Creutzfeldt-Jakob disease are accompanied by alterations in miRNA silencing machinery and biogenesis.* PLoS Pathog, 2018. **14**(1): p. e1006802.
164. Gibbings, D., et al., *Human prion protein binds Argonaute and promotes accumulation of microRNA effector complexes.* Nat Struct Mol Biol, 2012. **19**(5): p. 517-24, s1.
165. Vinken, P.J., G.W. Bruyn, and H.L. Klawans, *Handbook of clinical neurology.* 1968: Amsterdam : North-Holland, c1968-.
166. Myers, R.H., *Huntington's disease genetics.* NeuroRx, 2004. **1**(2): p. 255-62.
167. MacDonald, M.E., et al., *A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group.* Cell, 1993. **72**(6): p. 971-83.
168. Duyao, M., et al., *Trinucleotide repeat length instability and age of onset in Huntington's disease.* Nat Genet, 1993. **4**(4): p. 387-92.
169. Wilson, C.M., et al., *The Role of Endoproteolytic Processing in Neurodegeneration.* CNS Neurol Disord Drug Targets, 2016. **15**(10): p. 1222-1230.
170. Yamamoto, A., J.J. Lucas, and R. Hen, *Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease.* Cell, 2000. **101**(1): p. 57-66.
171. Nasir, J., et al., *Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes.* Cell, 1995. **81**(5): p. 811-23.
172. Rigamonti, D., et al., *Wild-type huntingtin protects from apoptosis upstream of caspase-3.* J Neurosci, 2000. **20**(10): p. 3705-13.

173. Nguyen, G.D., et al., *Selective roles of normal and mutant huntingtin in neural induction and early neurogenesis.* PLoS One, 2013. **8**(5): p. e64368.
174. Hodges, A., et al., *Regional and cellular gene expression changes in human Huntington's disease brain.* Hum Mol Genet, 2006. **15**(6): p. 965-77.
175. Zuccato, C., et al., *Widespread disruption of repressor element-1 silencing transcription factor/neuron-restrictive silencer factor occupancy at its target genes in Huntington's disease.* J Neurosci, 2007. **27**(26): p. 6972-83.
176. Zuccato, C., et al., *Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes.* Nat Genet, 2003. **35**(1): p. 76-83.
177. Johnson, R. and N.J. Buckley, *Gene dysregulation in Huntington's disease: REST, microRNAs and beyond.* Neuromolecular Med, 2009. **11**(3): p. 183-99.
178. Johnson, R., et al., *Regulation of neural macroRNAs by the transcriptional repressor REST.* Rna, 2009. **15**(1): p. 85-96.
179. Marti, E., et al., *A myriad of miRNA variants in control and Huntington's disease brain regions detected by massively parallel sequencing.* Nucleic Acids Res, 2010. **38**(20): p. 7219-35.
180. Kalathur, R.K., M.A. Hernandez-Prieto, and M.E. Futschik, *Huntington's disease and its therapeutic target genes: a global functional profile based on the HD Research Crossroads database.* BMC Neurol, 2012. **12**: p. 47.
181. Kumar, A., et al., *Huntington's disease: an update of therapeutic strategies.* Gene, 2015. **556**(2): p. 91-7.
182. Potkin, K.T. and S.G. Potkin, *New directions in therapeutics for Huntington disease.* Future Neurol, 2018. **13**(2): p. 101-121.
183. Shah, S.Z.A., et al., *Regulation of MicroRNAs-Mediated Autophagic Flux: A New Regulatory Avenue for Neurodegenerative Diseases With Focus on Prion Diseases.* Front Aging Neurosci, 2018. **10**: p. 139.
184. Chang, K.H., Y.R. Wu, and C.M. Chen, *Down-regulation of miR-9* in the peripheral leukocytes of Huntington's disease patients.* Orphanet J Rare Dis, 2017. **12**(1): p. 185.
185. Kocerha, J., et al., *microRNA-128a dysregulation in transgenic Huntington's disease monkeys.* Mol Brain, 2014. **7**: p. 46.
186. Wu, J. and X. Xie, *Comparative sequence analysis reveals an intricate network among REST, CREB and miRNA in mediating neuronal gene expression.* Genome Biol, 2006. **7**(9): p. R85.
187. Rowland, L.P. and N.A. Shneider, *Amyotrophic lateral sclerosis.* N Engl J Med, 2001. **344**(22): p. 1688-700.
188. Talbot, K., *Motor neuron disease: the bare essentials.* Pract Neurol, 2009. **9**(5): p. 303-9.
189. Pupillo, E., et al., *Long-term survival in amyotrophic lateral sclerosis: a population-based study.* Ann Neurol, 2014. **75**(2): p. 287-97.
190. Martin, S., A. Al Khleifat, and A. Al-Chalabi, *What causes amyotrophic lateral sclerosis?* F1000Res, 2017. **6**: p. 371.
191. Hughes, J.T., *Pathology of amyotrophic lateral sclerosis.* Adv Neurol, 1982. **36**: p. 61-74.
192. Goetz, C.G., *Amyotrophic lateral sclerosis: early contributions of Jean-Martin Charcot.* Muscle Nerve, 2000. **23**(3): p. 336-43.
193. Wijesekera, L.C. and P.N. Leigh, *Amyotrophic lateral sclerosis.* Orphanet J Rare Dis, 2009. **4**: p. 3.
194. Leigh, P.N., et al., *The management of motor neurone disease.* J Neurol Neurosurg Psychiatry, 2003. **74 Suppl 4**(Suppl 4): p. iv32-iv47.

195. Polkey, M.I., et al., *Respiratory aspects of neurological disease.* J Neurol Neurosurg Psychiatry, 1999. **66**(1): p. 5-15.
196. Handy, C.R., et al., *Pain in amyotrophic lateral sclerosis: a neglected aspect of disease.* Neurol Res Int, 2011. **2011**: p. 403808.
197. Al-Chalabi, A., L.H. van den Berg, and J. Veldink, *Gene discovery in amyotrophic lateral sclerosis: implications for clinical management.* Nat Rev Neurol, 2017. **13**(2): p. 96-104.
198. Liu, Z.J., et al., *Identify mutation in amyotrophic lateral sclerosis cases using HaloPlex target enrichment system.* Neurobiol Aging, 2014. **35**(12): p. 2881.e11-2881.e15.
199. Zarei, S., et al., *A comprehensive review of amyotrophic lateral sclerosis.* Surg Neurol Int, 2015. **6**: p. 171.
200. Tao, Q.Q. and Z.Y. Wu, *Amyotrophic Lateral Sclerosis: Precise Diagnosis and Individualized Treatment.* Chin Med J (Engl), 2017. **130**(19): p. 2269-2272.
201. Cui, B., et al., *Behavioral Symptoms in Motor Neuron Disease and Their Negative Impact on Caregiver Burden.* Chin Med J (Engl), 2015. **128**(17): p. 2295-300.
202. Rosen, D.R., *Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis.* Nature, 1993. **364**(6435): p. 362.
203. Neumann, M., et al., *Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis.* Science, 2006. **314**(5796): p. 130-3.
204. Arai, T., et al., *TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis.* Biochem Biophys Res Commun, 2006. **351**(3): p. 602-11.
205. Volk, A.E., et al., *Current knowledge and recent insights into the genetic basis of amyotrophic lateral sclerosis.* Med Genet, 2018. **30**(2): p. 252-258.
206. Walker, C., et al., *C9orf72 expansion disrupts ATM-mediated chromosomal break repair.* Nat Neurosci, 2017. **20**(9): p. 1225-1235.
207. Taylor, J.P., R.H. Brown, Jr., and D.W. Cleveland, *Decoding ALS: from genes to mechanism.* Nature, 2016. **539**(7628): p. 197-206.
208. Batra, G., et al., *Novel therapeutic targets for amyotrophic lateral sclerosis.* Indian J Pharmacol, 2019. **51**(6): p. 418-425.
209. García, M.L., A. Fernández, and M.T. Solas, *Mitochondria, motor neurons and aging.* J Neurol Sci, 2013. **330**(1-2): p. 18-26.
210. Ono, Y., et al., *SA4503, a sigma-1 receptor agonist, suppresses motor neuron damage in in vitro and in vivo amyotrophic lateral sclerosis models.* Neurosci Lett, 2014. **559**: p. 174-8.
211. Foran, E. and D. Trotti, *Glutamate transporters and the excitotoxic path to motor neuron degeneration in amyotrophic lateral sclerosis.* Antioxid Redox Signal, 2009. **11**(7): p. 1587-602.
212. Lin, C.L., et al., *Aberrant RNA processing in a neurodegenerative disease: the cause for absent EAAT2, a glutamate transporter, in amyotrophic lateral sclerosis.* Neuron, 1998. **20**(3): p. 589-602.
213. Blokhuis, A.M., et al., *Protein aggregation in amyotrophic lateral sclerosis.* Acta Neuropathol, 2013. **125**(6): p. 777-94.
214. Gagliardi, D., et al., *MicroRNAs as regulators of cell death mechanisms in amyotrophic lateral sclerosis.* J Cell Mol Med, 2019. **23**(3): p. 1647-1656.
215. Hardiman, O., L.H. van den Berg, and M.C. Kiernan, *Clinical diagnosis and management of amyotrophic lateral sclerosis.* Nat Rev Neurol, 2011. **7**(11): p. 639-49.

216. Lomen-Hoerth, C., T. Anderson, and B. Miller, *The overlap of amyotrophic lateral sclerosis and frontotemporal dementia.* Neurology, 2002. **59**(7): p. 1077-9.
217. Huang, Y., Z. Wu, and B. Zhou, *hSOD1 promotes tau phosphorylation and toxicity in the Drosophila model.* J Alzheimers Dis, 2015. **45**(1): p. 235-44.
218. Kiernan, J.A. and A.J. Hudson, *Frontal lobe atrophy in motor neuron diseases.* Brain, 1994. **117 (Pt 4)**: p. 747-57.
219. Strong, M.J., et al., *A prospective study of cognitive impairment in ALS.* Neurology, 1999. **53**(8): p. 1665-70.
220. Silverman, J.M., et al., *Disease Mechanisms in ALS: Misfolded SOD1 Transferred Through Exosome-Dependent and Exosome-Independent Pathways.* Cell Mol Neurobiol, 2016. **36**(3): p. 377-81.
221. Gomes, C., et al., *Evidence for secretion of Cu,Zn superoxide dismutase via exosomes from a cell model of amyotrophic lateral sclerosis.* Neurosci Lett, 2007. **428**(1): p. 43-6.
222. Grad, L.I., et al., *Intercellular propagated misfolding of wild-type Cu/Zn superoxide dismutase occurs via exosome-dependent and -independent mechanisms.* Proc Natl Acad Sci U S A, 2014. **111**(9): p. 3620-5.
223. Morgan, S. and R.W. Orrell, *Pathogenesis of amyotrophic lateral sclerosis.* Br Med Bull, 2016. **119**(1): p. 87-98.
224. Da Cruz, S. and D.W. Cleveland, *Understanding the role of TDP-43 and FUS/TLS in ALS and beyond.* Curr Opin Neurobiol, 2011. **21**(6): p. 904-19.
225. Kawahara, Y. and A. Mieda-Sato, *TDP-43 promotes microRNA biogenesis as a component of the Drosha and Dicer complexes.* Proc Natl Acad Sci U S A, 2012. **109**(9): p. 3347-52.
226. Morlando, M., et al., *FUS stimulates microRNA biogenesis by facilitating co-transcriptional Drosha recruitment.* Embo j, 2012. **31**(24): p. 4502-10.
227. Emde, A., et al., *Dysregulated miRNA biogenesis downstream of cellular stress and ALS-causing mutations: a new mechanism for ALS.* Embo j, 2015. **34**(21): p. 2633-51.
228. Bhadra, U., et al., *Tiny microRNAs Fine-Tune Amyotrophic Lateral Sclerosis Regulation.* 2016: IntechOpen.
229. Compston, A. and A. Coles, *Multiple sclerosis.* Lancet, 2008. **372**(9648): p. 1502-17.
230. Weinshenker, B.G., *Epidemiology of multiple sclerosis.* Neurol Clin, 1996. **14**(2): p. 291-308.
231. Brust, C.M., *Current diagnosis & treatment in neurology (2nd ed).* . 2012, McGraw-Hill Medical: New York.
232. Koch-Henriksen, N. and P.S. Sørensen, *The changing demographic pattern of multiple sclerosis epidemiology.* Lancet Neurol, 2010. **9**(5): p. 520-32.
233. Kurtzke, J.F., *Epidemiology of multiple sclerosis. Does this really point toward an etiology? Lectio Doctoralis.* Neurol Sci, 2000. **21**(6): p. 383-403.
234. Ghasemi, N., S. Razavi, and E. Nikzad, *Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy.* Cell J, 2017. **19**(1): p. 1-10.
235. de Sa, J.C., et al., *Symptomatic therapy in multiple sclerosis: a review for a multimodal approach in clinical practice.* Ther Adv Neurol Disord, 2011. **4**(3): p. 139-68.
236. Holland, B.E., *Factors affecting quality of life in persons with multiple sclerosis*, in *The University of Texas at Arlington*. 2014, The University of Texas: Texas. p. 116.
237. Huang, W.J., W.W. Chen, and X. Zhang, *Multiple sclerosis: Pathology, diagnosis and treatments.* Exp Ther Med, 2017. **13**(6): p. 3163-3166.
238. Hogancamp, W.E., M. Rodriguez, and B.G. Weinshenker, *The epidemiology of multiple sclerosis.* Mayo Clin Proc, 1997. **72**(9): p. 871-8.

239. Olek, M.J. *Epidemiology, risk factors and clinical features of multiple sclerosis in adults.* . 2019 [cited 4th June 2020.
240. Weiner, H.L., *A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis.* J Neurol, 2008. **255 Suppl 1**: p. 3-11.
241. Gandhi, R., A. Laroni, and H.L. Weiner, *Role of the innate immune system in the pathogenesis of multiple sclerosis.* J Neuroimmunol, 2010. **221**(1-2): p. 7-14.
242. Kasper, L.H. and J. Shoemaker, *Multiple sclerosis immunology: The healthy immune system vs the MS immune system.* Neurology, 2010. **74 Suppl 1**: p. S2-8.
243. Kouchaki, E., et al., *Numerical status of CD4(+)CD25(+)FoxP3(+) and CD8(+)CD28(-) regulatory T cells in multiple sclerosis.* Iran J Basic Med Sci, 2014. **17**(4): p. 250-5.
244. Olah, M., et al., *Identification of a microglia phenotype supportive of remyelination.* Glia, 2012. **60**(2): p. 306-21.
245. Roumier, A., et al., *Impaired synaptic function in the microglial KARAP/DAP12-deficient mouse.* J Neurosci, 2004. **24**(50): p. 11421-8.
246. Wake, H., et al., *Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals.* J Neurosci, 2009. **29**(13): p. 3974-80.
247. Blonda, M., et al., *Multiple Sclerosis Treatments Affect Monocyte-Derived Microvesicle Production.* Front Neurol, 2017. **8**: p. 422.
248. Roberts, C.T., Jr. and P. Kurre, *Vesicle trafficking and RNA transfer add complexity and connectivity to cell-cell communication.* Cancer Res, 2013. **73**(11): p. 3200-5.
249. Vickers, K.C. and A.T. Remaley, *Lipid-based carriers of microRNAs and intercellular communication.* Curr Opin Lipidol, 2012. **23**(2): p. 91-7.
250. Gallo, A., et al., *The majority of microRNAs detectable in serum and saliva is concentrated in exosomes.* PLoS One, 2012. **7**(3): p. e30679.
251. Kanada, M., et al., *Differential fates of biomolecules delivered to target cells via extracellular vesicles.* Proc Natl Acad Sci U S A, 2015. **112**(12): p. E1433-42.
252. Sáenz-Cuesta, M., I. Osorio-Querejeta, and D. Otaegui, *Extracellular Vesicles in Multiple Sclerosis: What are They Telling Us?* Front Cell Neurosci, 2014. **8**: p. 100.
253. Zare-Shahabadi, A., Y. Renaudineau, and N. Rezaei, *MicroRNAs and multiple sclerosis: from physiopathology toward therapy.* Expert Opin Ther Targets, 2013. **17**(12): p. 1497-507.
254. Jagot, F. and N. Davoust, *Is It worth Considering Circulating microRNAs in Multiple Sclerosis?* Front Immunol, 2016. **7**: p. 129.
255. Tufekci, K.U., et al., *MicroRNAs and Multiple Sclerosis.* Autoimmune Dis, 2010. **2011**: p. 807426.
256. Cheng, L.C., et al., *miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche.* Nat Neurosci, 2009. **12**(4): p. 399-408.
257. Du, C., et al., *MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis.* Nat Immunol, 2009. **10**(12): p. 1252-9.
258. Tautz, D., *Hypervariability of simple sequences as a general source for polymorphic DNA markers.* Nucleic Acids Res, 1989. **17**(16): p. 6463-71.
259. Mrázek, J., X. Guo, and A. Shah, *Simple sequence repeats in prokaryotic genomes.* Proc Natl Acad Sci U S A, 2007. **104**(20): p. 8472-7.
260. Tóth, G., Z. Gáspári, and J. Jurka, *Microsatellites in different eukaryotic genomes: survey and analysis.* Genome Res, 2000. **10**(7): p. 967-81.
261. Kovtun, I.V. and C.T. McMurray, *Features of trinucleotide repeat instability in vivo.* Cell Res, 2008. **18**(1): p. 198-213.

262. Gatchel, J.R. and H.Y. Zoghbi, *Diseases of unstable repeat expansion: mechanisms and common principles.* Nat Rev Genet, 2005. **6**(10): p. 743-55.
263. McMurray, C.T., *Mechanisms of trinucleotide repeat instability during human development.* Nat Rev Genet, 2010. **11**(11): p. 786-99.
264. Wells, R.D., *Molecular basis of genetic instability of triplet repeats.* J Biol Chem, 1996. **271**(6): p. 2875-8.
265. Cummings, C.J. and H.Y. Zoghbi, *Trinucleotide repeats: mechanisms and pathophysiology.* Annu Rev Genomics Hum Genet, 2000. **1**: p. 281-328.
266. Tan, H., Z. Xu, and P. Jin, *Role of noncoding RNAs in trinucleotide repeat neurodegenerative disorders.* Exp Neurol, 2012. **235**(2): p. 469-75.
267. Nakamori, M. and C. Thornton, *Epigenetic changes and non-coding expanded repeats.* Neurobiol Dis, 2010. **39**(1): p. 21-7.
268. Schaefer, M.H., E.E. Wanker, and M.A. Andrade-Navarro, *Evolution and function of CAG/polyglutamine repeats in protein-protein interaction networks.* Nucleic Acids Res, 2012. **40**(10): p. 4273-87.
269. Almeida, B., et al., *Trinucleotide repeats: a structural perspective.* Front Neurol, 2013. **4**: p. 76.
270. Orr, H.T. and H.Y. Zoghbi, *Trinucleotide repeat disorders.* Annu Rev Neurosci, 2007. **30**: p. 575-621.
271. Murmann, A.E., et al., *Trinucleotide Repeat Expansion Diseases, RNAi, and Cancer.* Trends Cancer, 2018. **4**(10): p. 684-700.
272. Hoss, A.G., et al., *miR-10b-5p expression in Huntington's disease brain relates to age of onset and the extent of striatal involvement.* BMC Med Genomics, 2015. **8**: p. 10.
273. Pyrkova, A.Y., A.T. Ivashchenko, and B. O.A., *Parallelization of scanning genes on the cluster platform: MirTarget program*, s.m. KazNU Bulletin, mech., inf. 2014, , Editor. 2014.
274. Belkozhayev, A.M., R.E. Niyazova, and A.T. Ivashchenko, *The prediction of miRNAs binding sites in CDS mRNA genes having trinucleotide repeats.* Experimental Biology, 2019. **79**(2): p. 64-74.
275. Health, N.I.o. *Resource for stem cell research.* 2008 4th June 2020].
276. Ma, D.K., et al., *Adult neural stem cells in the mammalian central nervous system.* Cell Res, 2009. **19**(6): p. 672-82.
277. Drukker, M., et al., *Characterization of the expression of MHC proteins in human embryonic stem cells.* Proc Natl Acad Sci U S A, 2002. **99**(15): p. 9864-9.
278. Biehl, J.K. and B. Russell, *Introduction to stem cell therapy.* J Cardiovasc Nurs, 2009. **24**(2): p. 98-103; quiz 104-5.
279. Jaenisch, R. and R. Young, *Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming.* Cell, 2008. **132**(4): p. 567-82.
280. Marson, A., et al., *Connecting microRNA genes to the core transcriptional regulatory circuitry of embryonic stem cells.* Cell, 2008. **134**(3): p. 521-33.
281. Alhadlaq, A. and J.J. Mao, *Tissue-engineered osteochondral constructs in the shape of an articular condyle.* J Bone Joint Surg Am, 2005. **87**(5): p. 936-44.
282. Madrazo, I., et al., *Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease.* N Engl J Med, 1987. **316**(14): p. 831-4.
283. Barker, R.A., et al., *Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era.* Cell Stem Cell, 2017. **21**(5): p. 569-573.
284. Kirkeby, A., M. Parmar, and R.A. Barker, *Strategies for bringing stem cell-derived dopamine neurons to the clinic: A European approach (STEM-PD).* Prog Brain Res, 2017. **230**: p. 165-190.

285. Yu, D.X., M.C. Marchetto, and F.H. Gage, *Therapeutic translation of iPSCs for treating neurological disease.* Cell Stem Cell, 2013. **12**(6): p. 678-88.
286. Kang, J.M., et al., *Stem Cell Therapy for Alzheimer's Disease: A Review of Recent Clinical Trials.* J Alzheimers Dis, 2016. **54**(3): p. 879-889.
287. Xuan, A.G., et al., *Effects of engrafted neural stem cells in Alzheimer's disease rats.* Neurosci Lett, 2009. **450**(2): p. 167-71.
288. Marks, P.W., C.M. Witten, and R.M. Califf, *Clarifying Stem-Cell Therapy's Benefits and Risks.* N Engl J Med, 2017. **376**(11): p. 1007-1009.
289. Stuckey, D.W. and K. Shah, *Stem cell-based therapies for cancer treatment: separating hope from hype.* Nat Rev Cancer, 2014. **14**(10): p. 683-91.
290. Granero-Molto, F., et al., *Role of mesenchymal stem cells in regenerative medicine: application to bone and cartilage repair.* Expert Opin Biol Ther, 2008. **8**(3): p. 255-68.
291. Wei, X., et al., *Mesenchymal stem cells: a new trend for cell therapy.* Acta Pharmacol Sin, 2013. **34**(6): p. 747-54.
292. Siniscalco, D., et al., *Intra-brain microinjection of human mesenchymal stem cells decreases allodynia in neuropathic mice.* Cell Mol Life Sci, 2010. **67**(4): p. 655-69.
293. Teixeira, F.G., et al., *Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration?* Cell Mol Life Sci, 2013. **70**(20): p. 3871-82.
294. Castorina, A., et al., *Mesenchymal stem cells-based therapy as a potential treatment in neurodegenerative disorders: is the escape from senescence an answer?* Neural Regen Res, 2015. **10**(6): p. 850-8.
295. Li, Y., et al., *Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery.* Neurology, 2002. **59**(4): p. 514-23.
296. Lu, D., A. Mahmood, and M. Chopp, *Biologic transplantation and neurotrophin-induced neuroplasticity after traumatic brain injury.* J Head Trauma Rehabil, 2003. **18**(4): p. 357-76.
297. Mahmood, A., D. Lu, and M. Chopp, *Intravenous administration of marrow stromal cells (MSCs) increases the expression of growth factors in rat brain after traumatic brain injury.* J Neurotrauma, 2004. **21**(1): p. 33-9.
298. Chen, X., et al., *Human bone marrow stromal cell cultures conditioned by traumatic brain tissue extracts: growth factor production.* J Neurosci Res, 2002. **69**(5): p. 687-91.
299. Xin, H., et al., *Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth.* Stem Cells, 2012. **30**(7): p. 1556-64.
300. Xin, H., et al., *Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats.* J Cereb Blood Flow Metab, 2013. **33**(11): p. 1711-5.
301. Baek, G., et al., *Mesenchymal Stem Cell-Derived Extracellular Vesicles as Therapeutics and as a Drug Delivery Platform.* Stem Cells Transl Med, 2019. **8**(9): p. 880-886.
302. Vakhshiteh, F., F. Atyabi, and S.N. Ostad, *Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy.* Int J Nanomedicine, 2019. **14**: p. 2847-2859.
303. Grange, C., et al., *Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche.* Cancer Res, 2011. **71**(15): p. 5346-56.
304. Lee, H.K., et al., *Mesenchymal stem cells deliver synthetic microRNA mimics to glioma cells and glioma stem cells and inhibit their cell migration and self-renewal.* Oncotarget, 2013. **4**(2): p. 346-61.

305. La Spada, A.R. and J.P. Taylor, *Repeat expansion disease: progress and puzzles in disease pathogenesis.* Nat Rev Genet, 2010. **11**(4): p. 247-58.
306. Krzyzosiak, W.J., et al., *Triplet repeat RNA structure and its role as pathogenic agent and therapeutic target.* Nucleic Acids Res, 2012. **40**(1): p. 11-26.
307. Kozlowski, P., M. de Mezer, and W.J. Krzyzosiak, *Trinucleotide repeats in human genome and exome.* Nucleic Acids Res, 2010. **38**(12): p. 4027-39.
308. van der Krol, A.R., et al., *Flavonoid genes in petunia: addition of a limited number of gene copies may lead to a suppression of gene expression.* Plant Cell, 1990. **2**(4): p. 291-9.
309. García-López, A., et al., *In vivo discovery of a peptide that prevents CUG-RNA hairpin formation and reverses RNA toxicity in myotonic dystrophy models.* Proc Natl Acad Sci U S A, 2011. **108**(29): p. 11866-71.
310. Gareiss, P.C., et al., *Dynamic combinatorial selection of molecules capable of inhibiting the (CUG) repeat RNA-MBNL1 interaction in vitro: discovery of lead compounds targeting myotonic dystrophy (DM1).* J Am Chem Soc, 2008. **130**(48): p. 16254-61.
311. Warf, M.B., et al., *Pentamidine reverses the splicing defects associated with myotonic dystrophy.* Proc Natl Acad Sci U S A, 2009. **106**(44): p. 18551-6.
312. Harper, S.Q., et al., *RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model.* Proc Natl Acad Sci U S A, 2005. **102**(16): p. 5820-5.
313. Boudreau, R.L., et al., *Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice.* Mol Ther, 2009. **17**(6): p. 1053-63.
314. Verma, A.K., et al., *Exploring the Potential of Small Molecule-Based Therapeutic Approaches for Targeting Trinucleotide Repeat Disorders.* Mol Neurobiol, 2020. **57**(1): p. 566-584.
315. Campuzano, V., et al., *Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion.* Science, 1996. **271**(5254): p. 1423-7.
316. Soragni, E., et al., *Epigenetic therapy for Friedreich ataxia.* Ann Neurol, 2014. **76**(4): p. 489-508.
317. Libri, V., et al., *Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study.* Lancet, 2014. **384**(9942): p. 504-13.
318. Sahdeo, S., et al., *Dyclonine rescues frataxin deficiency in animal models and buccal cells of patients with Friedreich's ataxia.* Hum Mol Genet, 2014. **23**(25): p. 6848-62.
319. Perdomini, M., et al., *Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia.* Nat Med, 2014. **20**(5): p. 542-7.
320. Wyttenbach, A., *Role of heat shock proteins during polyglutamine neurodegeneration: mechanisms and hypothesis.* J Mol Neurosci, 2004. **23**(1-2): p. 69-96.
321. Muchowski, P.J. and J.L. Wacker, *Modulation of neurodegeneration by molecular chaperones.* Nat Rev Neurosci, 2005. **6**(1): p. 11-22.
322. Agrawal, N., et al., *Identification of combinatorial drug regimens for treatment of Huntington's disease using Drosophila.* Proc Natl Acad Sci U S A, 2005. **102**(10): p. 3777-81.
323. Ehrnhoefer, D.E., et al., *Green tea (-)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models.* Hum Mol Genet, 2006. **15**(18): p. 2743-51.

324. Burke, J.R., et al., *The Haw River syndrome: dentatorubropallidoluysian atrophy (DRPLA) in an African-American family.* Nat Genet, 1994. **7**(4): p. 521-4.
325. Naito, H. and S. Oyanagi, *Familial myoclonus epilepsy and choreoathetosis: hereditary dentatorubral-pallidoluysian atrophy.* Neurology, 1982. **32**(8): p. 798-807.
326. Hu, J., et al., *Allele-selective inhibition of mutant atrophin-1 expression by duplex and single-stranded RNAs.* Biochemistry, 2014. **53**(28): p. 4510-8.
327. LoRusso, S., B. Weiner, and W.D. Arnold, *Myotonic Dystrophies: Targeting Therapies for Multisystem Disease.* Neurotherapeutics, 2018. **15**(4): p. 872-884.
328. Wang, Q., D.D. Mosser, and J. Bag, *Induction of HSP70 expression and recruitment of HSC70 and HSP70 in the nucleus reduce aggregation of a polyalanine expansion mutant of PABPN1 in HeLa cells.* Hum Mol Genet, 2005. **14**(23): p. 3673-84.
329. Cogswell, J.P., et al., *Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways.* J Alzheimers Dis, 2008. **14**(1): p. 27-41.
330. Klein, M.E., et al., *Homeostatic regulation of MeCP2 expression by a CREB-induced microRNA.* Nat Neurosci, 2007. **10**(12): p. 1513-4.
331. Smith, P.Y., et al., *MicroRNA-132 loss is associated with tau exon 10 inclusion in progressive supranuclear palsy.* Hum Mol Genet, 2011. **20**(20): p. 4016-24.
332. An, F., et al., *MiR-124 acts as a target for Alzheimer's disease by regulating BACE1.* Oncotarget, 2017. **8**(69): p. 114065-114071.
333. Hébert, S.S., et al., *Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression.* Proc Natl Acad Sci U S A, 2008. **105**(17): p. 6415-20.
334. Madadi, S., et al., *Downregulation of serum miR-106b: a potential biomarker for Alzheimer disease.* Arch Physiol Biochem, 2020: p. 1-5.
335. Liu, C.G., et al., *MicroRNA-135a and -200b, potential Biomarkers for Alzheimer's disease, regulate β secretase and amyloid precursor protein.* Brain Res, 2014. **1583**: p. 55-64.
336. Yang, T.T., et al., *The Serum Exosome Derived MicroRNA-135a, -193b, and -384 Were Potential Alzheimer's Disease Biomarkers.* Biomed Environ Sci, 2018. **31**(2): p. 87-96.
337. Lukiw, W.J., et al., *Spreading of Alzheimer's disease inflammatory signaling through soluble micro-RNA.* Neuroreport, 2012. **23**(10): p. 621-6.
338. Sierksma, A., et al., *Deregulation of neuronal miRNAs induced by amyloid-β or TAU pathology.* Mol Neurodegener, 2018. **13**(1): p. 54.
339. Li, T.R., et al., *The role of the microRNA-146a/complement factor H/interleukin-1β-mediated inflammatory loop circuit in the perpetuate inflammation of chronic temporal lobe epilepsy.* Dis Model Mech, 2018. **11**(3).
340. Long, J.M., B. Ray, and D.K. Lahiri, *MicroRNA-153 physiologically inhibits expression of amyloid-β precursor protein in cultured human fetal brain cells and is dysregulated in a subset of Alzheimer disease patients.* J Biol Chem, 2012. **287**(37): p. 31298-310.
341. Wang, H., et al., *Multiple roles of microRNA-146a in immune responses and hepatocellular carcinoma.* Oncol Lett, 2019. **18**(5): p. 5033-5042.
342. Kou, X., D. Chen, and N. Chen, *The Regulation of microRNAs in Alzheimer's Disease.* Frontiers in Neurology, 2020. **11**(288).
343. Parsi, S., et al., *Preclinical Evaluation of miR-15/107 Family Members as Multifactorial Drug Targets for Alzheimer's Disease.* Mol Ther Nucleic Acids, 2015. **4**(10): p. e256.

344. Hébert, S.S., et al., *MicroRNA regulation of Alzheimer's Amyloid precursor protein expression.* Neurobiol Dis, 2009. **33**(3): p. 422-8.
345. Delay, C., et al., *Alzheimer-specific variants in the 3'UTR of Amyloid precursor protein affect microRNA function.* Mol Neurodegener, 2011. **6**: p. 70.
346. Tan, L., et al., *Circulating miR-125b as a biomarker of Alzheimer's disease.* J Neurol Sci, 2014. **336**(1-2): p. 52-6.
347. Geekiyanage, H. and C. Chan, *MicroRNA-137/181c regulates serine palmitoyltransferase and in turn amyloid β, novel targets in sporadic Alzheimer's disease.* J Neurosci, 2011. **31**(41): p. 14820-30.
348. Boissonneault, V., et al., *MicroRNA-298 and microRNA-328 regulate expression of mouse beta-amyloid precursor protein-converting enzyme 1.* J Biol Chem, 2009. **284**(4): p. 1971-81.
349. O'Brien, R.J. and P.C. Wong, *Amyloid precursor protein processing and Alzheimer's disease.* Annu Rev Neurosci, 2011. **34**: p. 185-204.
350. Wang, M., L. Qin, and B. Tang, *MicroRNAs in Alzheimer's Disease.* Frontiers in Genetics, 2019. **10**(153).
351. Wang, X., et al., *A Novel MicroRNA-124/PTPN1 Signal Pathway Mediates Synaptic and Memory Deficits in Alzheimer's Disease.* Biol Psychiatry, 2018. **83**(5): p. 395-405.
352. Smirnova, L., et al., *Regulation of miRNA expression during neural cell specification.* Eur J Neurosci, 2005. **21**(6): p. 1469-77.
353. Cao, J., et al., *MicroRNA-195 rescues ApoE4-induced cognitive deficits and lysosomal defects in Alzheimer's disease pathogenesis.* Mol Psychiatry, 2020.
354. Kole, A.J., et al., *miR-29b is activated during neuronal maturation and targets BH3-only genes to restrict apoptosis.* Genes Dev, 2011. **25**(2): p. 125-30.
355. Sarkar, S., et al., *Expression of microRNA-34a in Alzheimer's disease brain targets genes linked to synaptic plasticity, energy metabolism, and resting state network activity.* Brain Res, 2016. **1646**: p. 139-151.
356. Higaki, S., et al., *Defensive effect of microRNA-200b/c against amyloid-beta peptide-induced toxicity in Alzheimer's disease models.* PLoS One, 2018. **13**(5): p. e0196929.
357. Fu, J., et al., *Regulatory roles of the miR-200 family in neurodegenerative diseases.* Biomed Pharmacother, 2019. **119**: p. 109409.
358. Alvarez-Erviti, L., et al., *Influence of microRNA deregulation on chaperone-mediated autophagy and α-synuclein pathology in Parkinson's disease.* Cell Death Dis, 2013. **4**(3): p. e545.
359. Zhang, Z. and Y. Cheng, *miR-16-1 promotes the aberrant α-synuclein accumulation in parkinson disease via targeting heat shock protein 70.* ScientificWorldJournal, 2014. **2014**: p. 938348.
360. Wang, Z.H., et al., *MicroRNA-214 participates in the neuroprotective effect of Resveratrol via inhibiting α-synuclein expression in MPTP-induced Parkinson's disease mouse.* Biomed Pharmacother, 2015. **74**: p. 252-6.
361. Recasens, A., C. Perier, and C.M. Sue, *Role of microRNAs in the Regulation of α-Synuclein Expression: A Systematic Review.* Front Mol Neurosci, 2016. **9**: p. 128.
362. Zhao, L. and Z. Wang, *MicroRNAs: Game Changers in the Regulation of α-Synuclein in Parkinson's Disease.* Parkinsons Dis, 2019. **2019**: p. 1743183.
363. Dong, H., et al., *A panel of four decreased serum microRNAs as a novel biomarker for early Parkinson's disease.* Biomarkers, 2016. **21**(2): p. 129-37.
364. Tatura, R., et al., *Parkinson's disease: SNCA-, PARK2-, and LRRK2- targeting microRNAs elevated in cingulate gyrus.* Parkinsonism Relat Disord, 2016. **33**: p. 115-121.

365. Prajapati, P., et al., *TNF-α regulates miRNA targeting mitochondrial complex-I and induces cell death in dopaminergic cells.* Biochim Biophys Acta, 2015. **1852**(3): p. 451-61.
366. Junn, E., et al., *Repression of alpha-synuclein expression and toxicity by microRNA-7.* Proc Natl Acad Sci U S A, 2009. **106**(31): p. 13052-7.
367. Zhou, Y., et al., *MicroRNA-7 targets Nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson's disease.* Mol Neurodegener, 2016. **11**: p. 28.
368. Kabaria, S., et al., *MicroRNA-7 activates Nrf2 pathway by targeting Keap1 expression.* Free Radic Biol Med, 2015. **89**: p. 548-56.
369. Chaudhuri, A.D., et al., *MicroRNA-7 Regulates the Function of Mitochondrial Permeability Transition Pore by Targeting VDAC1 Expression.* J Biol Chem, 2016. **291**(12): p. 6483-93.
370. Doxakis, E., *Post-transcriptional regulation of alpha-synuclein expression by mir-7 and mir-153.* J Biol Chem, 2010. **285**(17): p. 12726-34.
371. Decressac, M., et al., *TFEB-mediated autophagy rescues midbrain dopamine neurons from α-synuclein toxicity.* Proc Natl Acad Sci U S A, 2013. **110**(19): p. E1817-26.
372. Xiong, R., et al., *MicroRNA-494 reduces DJ-1 expression and exacerbates neurodegeneration.* Neurobiol Aging, 2014. **35**(3): p. 705-14.
373. Cho, H.J., et al., *MicroRNA-205 regulates the expression of Parkinson's disease-related leucine-rich repeat kinase 2 protein.* Hum Mol Genet, 2013. **22**(3): p. 608-20.
374. Cardo, L.F., et al., *The screening of the 3'UTR sequence of LRRK2 identified an association between the rs66737902 polymorphism and Parkinson's disease.* J Hum Genet, 2014. **59**(6): p. 346-8.
375. Freischmidt, A., et al., *Systemic dysregulation of TDP-43 binding microRNAs in amyotrophic lateral sclerosis.* Acta Neuropathol Commun, 2013. **1**: p. 42.
376. Waller, R., et al., *Small RNA Sequencing of Sporadic Amyotrophic Lateral Sclerosis Cerebrospinal Fluid Reveals Differentially Expressed miRNAs Related to Neural and Glial Activity.* Front Neurosci, 2017. **11**: p. 731.
377. Taguchi, Y.H. and H. Wang, *Exploring microRNA Biomarker for Amyotrophic Lateral Sclerosis.* Int J Mol Sci, 2018. **19**(5).
378. Kovanda, A., et al., *Differential expression of microRNAs and other small RNAs in muscle tissue of patients with ALS and healthy age-matched controls.* Sci Rep, 2018. **8**(1): p. 5609.
379. Vistbakka, J., et al., *Circulating microRNAs as biomarkers in progressive multiple sclerosis.* Mult Scler, 2017. **23**(3): p. 403-412.
380. D'Erchia, A.M., et al., *Massive transcriptome sequencing of human spinal cord tissues provides new insights into motor neuron degeneration in ALS.* Sci Rep, 2017. **7**(1): p. 10046.
381. Recabarren-Leiva, D. and M. Alarcón, *New insights into the gene expression associated to amyotrophic lateral sclerosis.* Life Sci, 2018. **193**: p. 110-123.
382. Liguori, M., et al., *Dysregulation of MicroRNAs and Target Genes Networks in Peripheral Blood of Patients With Sporadic Amyotrophic Lateral Sclerosis.* Front Mol Neurosci, 2018. **11**: p. 288.
383. Liguori, M., et al., *Combined microRNA and mRNA expression analysis in pediatric multiple sclerosis: an integrated approach to uncover novel pathogenic mechanisms of the disease.* Hum Mol Genet, 2018. **27**(1): p. 66-79.
384. Satoh, J., Y. Kino, and S. Niida, *MicroRNA-Seq Data Analysis Pipeline to Identify Blood Biomarkers for Alzheimer's Disease from Public Data.* Biomark Insights, 2015. **10**: p. 21-31.

385. Di Pietro, L., W. Lattanzi, and C. Bernardini, *Skeletal Muscle MicroRNAs as Key Players in the Pathogenesis of Amyotrophic Lateral Sclerosis.* Int J Mol Sci, 2018. **19**(5).
386. Ebrahimkhani, S., et al., *Exosomal microRNA signatures in multiple sclerosis reflect disease status.* Sci Rep, 2017. **7**(1): p. 14293.
387. Chang, W.S., et al., *Genome-Wide Profiling of miRNA and mRNA Expression in Alzheimer's Disease.* Med Sci Monit, 2017. **23**: p. 2721-2731.
388. Si, Y., et al., *Muscle microRNA signatures as biomarkers of disease progression in amyotrophic lateral sclerosis.* Neurobiol Dis, 2018. **114**: p. 85-94.
389. Raheja, R., et al., *Correlating serum micrornas and clinical parameters in amyotrophic lateral sclerosis.* Muscle Nerve, 2018. **58**(2): p. 261-269.
390. Devier, D.J., J.F. Lovera, and W.J. Lukiw, *Increase in NF-κB-sensitive miRNA-146a and miRNA-155 in multiple sclerosis (MS) and pro-inflammatory neurodegeneration.* Front Mol Neurosci, 2015. **8**: p. 5.
391. Wu, T. and G. Chen, *miRNAs Participate in MS Pathological Processes and Its Therapeutic Response.* Mediators Inflamm, 2016. **2016**: p. 4578230.
392. Hu, Z., et al., *Silencing miR-150 Ameliorates Experimental Autoimmune Encephalomyelitis.* Front Neurosci, 2018. **12**: p. 465.
393. Noorbakhsh, F., et al., *Impaired neurosteroid synthesis in multiple sclerosis.* Brain, 2011. **134**(Pt 9): p. 2703-21.
394. Dolati, S., et al., *Dysregulated Network of miRNAs Involved in the Pathogenesis of Multiple Sclerosis.* Biomed Pharmacother, 2018. **104**: p. 280-290.
395. Groen, K., et al., *Erythrocyte microRNA sequencing reveals differential expression in relapsing-remitting multiple sclerosis.* BMC Med Genomics, 2018. **11**(1): p. 48.
396. Witte, M.E., et al., *Reduced expression of PGC-1α partly underlies mitochondrial changes and correlates with neuronal loss in multiple sclerosis cortex.* Acta Neuropathol, 2013. **125**(2): p. 231-43.
397. Zhang, Q., et al., *MiR-30b-5p regulates the lipid metabolism by targeting PPARGC1A in Huh-7 cell line.* Lipids Health Dis, 2020. **19**(1): p. 76.
398. Tavakolpour, V., et al., *Increased expression of mir-301a in PBMCs of patients with relapsing-remitting multiple sclerosis is associated with reduced NKRF and PIAS3 expression levels and disease activity.* J Neuroimmunol, 2018. **325**: p. 79-86.
399. Ma, X., et al., *Expression, regulation and function of microRNAs in multiple sclerosis.* Int J Med Sci, 2014. **11**(8): p. 810-8.
400. Fenoglio, C., et al., *Decreased circulating miRNA levels in patients with primary progressive multiple sclerosis.* Mult Scler, 2013. **19**(14): p. 1938-42.
401. Junker, A., et al., *MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47.* Brain, 2009. **132**(Pt 12): p. 3342-52.
402. Mycko, M.P., et al., *miR-155-3p Drives the Development of Autoimmune Demyelination by Regulation of Heat Shock Protein 40.* J Neurosci, 2015. **35**(50): p. 16504-15.
403. Liu, S.Q., et al., *miR-17-92 cluster targets phosphatase and tensin homology and Ikaros Family Zinc Finger 4 to promote TH17-mediated inflammation.* J Biol Chem, 2014. **289**(18): p. 12446-56.
404. Ichiyama, K., et al., *The MicroRNA-183-96-182 Cluster Promotes T Helper 17 Cell Pathogenicity by Negatively Regulating Transcription Factor Foxo1 Expression.* Immunity, 2016. **44**(6): p. 1284-98.
405. Hanieh, H. and A. Alzahrani, *MicroRNA-132 suppresses autoimmune encephalomyelitis by inducing cholinergic anti-inflammation: a new Ahr-based exploration.* Eur J Immunol, 2013. **43**(10): p. 2771-82.

406. Nuzziello, N., et al., *Investigating the Role of MicroRNA and Transcription Factor Co-regulatory Networks in Multiple Sclerosis Pathogenesis.* Int J Mol Sci, 2018. **19**(11).
407. Mailleux, J., et al., *Active liver X receptor signaling in phagocytes in multiple sclerosis lesions.* Mult Scler, 2018. **24**(3): p. 279-289.
408. Zhou, Q., et al., *The Golgi-Associated Plant Pathogenesis-Related Protein GAPR-1 Enhances Type I Interferon Signaling Pathway in Response to Toll-Like Receptor 4.* Inflammation, 2016. **39**(2): p. 706-17.
409. Song, B., et al., *Neural differentiation of patient specific iPS cells as a novel approach to study the pathophysiology of multiple sclerosis.* Stem Cell Res, 2012. **8**(2): p. 259-73.
410. Zhao, Y., et al., *Regulation of TREM2 expression by an NF-κB-sensitive miRNA-34a.* Neuroreport, 2013. **24**(6): p. 318-23.
411. Zhao, Y., V. Jaber, and W.J. Lukiw, *Over-Expressed Pathogenic miRNAs in Alzheimer's Disease (AD) and Prion Disease (PrD) Drive Deficits in TREM2-Mediated Aβ42 Peptide Clearance.* Front Aging Neurosci, 2016. **8**: p. 140.
412. Saba, R., et al., *A miRNA signature of prion induced neurodegeneration.* PLoS One, 2008. **3**(11): p. e3652.
413. Montag, J., et al., *Upregulation of miRNA hsa-miR-342-3p in experimental and idiopathic prion disease.* Mol Neurodegener, 2009. **4**: p. 36.
414. Thackray, A.M., et al., *Transcriptional signature of prion-induced neurotoxicity in a Drosophila model of transmissible mammalian prion disease.* Biochem J, 2020. **477**(4): p. 833-852.
415. Tai, M.C., et al., *miR-342-3p regulates MYC transcriptional activity via direct repression of E2F1 in human lung cancer.* Carcinogenesis, 2015. **36**(12): p. 1464-73.
416. Cui, J.G., et al., *Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-kappaB in stressed human astroglial cells and in Alzheimer disease.* J Biol Chem, 2010. **285**(50): p. 38951-60.
417. Lukiw, W.J., et al., *Upregulation of micro RNA-146a (miRNA-146a), a marker for inflammatory neurodegeneration, in sporadic Creutzfeldt-Jakob disease (sCJD) and Gerstmann-Straussler-Scheinker (GSS) syndrome.* J Toxicol Environ Health A, 2011. **74**(22-24): p. 1460-8.
418. Alleaume-Butaux, A., et al., *Double-Edge Sword of Sustained ROCK Activation in Prion Diseases through Neuritogenesis Defects and Prion Accumulation.* PLoS Pathog, 2015. **11**(8): p. e1005073.
419. Feng, B. and S. Chakrabarti, *miR-320 Regulates Glucose-Induced Gene Expression in Diabetes.* ISRN Endocrinol, 2012. **2012**: p. 549875.
420. LaCasse, R.A., et al., *Role of Erk1/2 activation in prion disease pathogenesis: absence of CCR1 leads to increased Erk1/2 activation and accelerated disease progression.* J Neuroimmunol, 2008. **196**(1-2): p. 16-26.
421. Caetano, F.A., et al., *Endocytosis of prion protein is required for ERK1/2 signaling induced by stress-inducible protein 1.* J Neurosci, 2008. **28**(26): p. 6691-702.
422. Relaño-Ginés, A., S. Lehmann, and C. Crozet, *Prion diseases and adult neurogenesis: how do prions counteract the brain's endogenous repair machinery?* Prion, 2014. **8**(3): p. 240-6.
423. Evangelisti, C., et al., *MiR-128 up-regulation inhibits Reelin and DCX expression and reduces neuroblastoma cell motility and invasiveness.* Faseb j, 2009. **23**(12): p. 4276-87.
424. Han, N., et al., *MiR-328 suppresses the survival of esophageal cancer cells by targeting PLCE1.* Biochem Biophys Res Commun, 2016. **470**(1): p. 175-180.

425. Llorens, F., et al., *Regional and subtype-dependent miRNA signatures in sporadic Creutzfeldt-Jakob disease are accompanied by alterations in miRNA silencing machinery and biogenesis.* PLoS Pathog, 2018. **14**(1): p. e1006802.
426. Fan, X.Y., et al., *Activation of the AMPK-ULK1 pathway plays an important role in autophagy during prion infection.* Sci Rep, 2015. **5**: p. 14728.
427. Hao, Z. and G. Wang, *Autophagy and Prion Disease.* Adv Exp Med Biol, 2020. **1207**: p. 75-85.
428. Burak, K., et al., *MicroRNA-16 targets mRNA involved in neurite extension and branching in hippocampal neurons during presymptomatic prion disease.* Neurobiol Dis, 2018. **112**: p. 1-13.
429. Norsworthy, P.J., et al., *A blood miRNA signature associates with sporadic Creutzfeldt-Jakob disease diagnosis.* Nat Commun, 2020. **11**(1): p. 3960.
430. Yang, Y.T. and S. Jin, *Effect of PrP105-132 on the secretion of interleukin-6 and interleukin-8 from microglial cells in vitro.* Exp Ther Med, 2018. **15**(1): p. 999-1004.
431. Fabbri, E., et al., *MicroRNA miR-93-5p regulates expression of IL-8 and VEGF in neuroblastoma SK-N-AS cells.* Oncol Rep, 2016. **35**(5): p. 2866-72.
432. Xiong, J., et al., *An estrogen receptor alpha suppressor, microRNA-22, is downregulated in estrogen receptor alpha-positive human breast cancer cell lines and clinical samples.* Febs j, 2010. **277**(7): p. 1684-94.
433. Jovicic, A., et al., *MicroRNA-22 (miR-22) overexpression is neuroprotective via general anti-apoptotic effects and may also target specific Huntington's disease-related mechanisms.* PLoS One, 2013. **8**(1): p. e54222.
434. Chen, D., et al., *The Role of MiR-132 in Regulating Neural Stem Cell Proliferation, Differentiation and Neuronal Maturation.* Cell Physiol Biochem, 2018. **47**(6): p. 2319-2330.
435. Makeyev, E.V., et al., *The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing.* Mol Cell, 2007. **27**(3): p. 435-48.
436. Liu, T., et al., *MicroRNA-124 slows down the progression of Huntington's disease by promoting neurogenesis in the striatum.* Neural Regen Res, 2015. **10**(5): p. 786-91.
437. Moumné, L., S. Betuing, and J. Caboche, *Multiple Aspects of Gene Dysregulation in Huntington's Disease.* Front Neurol, 2013. **4**: p. 127.
438. Tan, L., J.T. Yu, and L. Tan, *Causes and Consequences of MicroRNA Dysregulation in Neurodegenerative Diseases.* Mol Neurobiol, 2015. **51**(3): p. 1249-62.
439. Kunkanjanawan, T., et al., *miR-196a Ameliorates Cytotoxicity and Cellular Phenotype in Transgenic Huntington's Disease Monkey Neural Cells.* PLoS One, 2016. **11**(9): p. e0162788.
440. Hoss, A.G., et al., *Study of plasma-derived miRNAs mimic differences in Huntington's disease brain.* Mov Disord, 2015. **30**(14): p. 1961-4.
441. Jamwal, S. and P. Kumar, *Antidepressants for neuroprotection in Huntington's disease: A review.* Eur J Pharmacol, 2015. **769**: p. 33-42.
442. Lewis, B.P., C.B. Burge, and D.P. Bartel, *Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets.* Cell, 2005. **120**(1): p. 15-20.
443. Sonkoly, E., M. Ståhle, and A. Pivarcsi, *MicroRNAs and immunity: novel players in the regulation of normal immune function and inflammation.* Semin Cancer Biol, 2008. **18**(2): p. 131-40.
444. Sinha, M., et al., *Altered microRNAs in STHdh(Q111)/Hdh(Q111) cells: miR-146a targets TBP.* Biochem Biophys Res Commun, 2010. **396**(3): p. 742-7.

445. Laprairie, R.B., et al., *Huntington's disease pattern of transcriptional dysregulation in the absence of mutant huntingtin is produced by knockout of neuronal GLT-1.* Neurochem Int, 2019. **123**: p. 85-94.
446. Sinha, M., J. Ghose, and N.P. Bhattarcharyya, *Micro RNA -214,-150,-146a and-125b target Huntingtin gene.* RNA Biol, 2011. **8**(6): p. 1005-21.
447. Kozlowska, E., W.J. Krzyzosiak, and E. Koscianska, *Regulation of huntingtin gene expression by miRNA-137, -214, -148a, and their respective isomiRs.* Int J Mol Sci, 2013. **14**(8): p. 16999-7016.
448. Hoss, A.G., et al., *MicroRNAs located in the Hox gene clusters are implicated in huntington's disease pathogenesis.* PLoS Genet, 2014. **10**(2): p. e1004188.
449. Trials.gov, C. *The Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease*. 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT04388982?term=exosome&cond=Alzheimer+Disease&draw=2&rank=1.
450. Trial.gov, C. *Cardiac Changes in Early Parkinson's Disease: A Follow up Study*. 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT04218968?term=EVs&cond=Parkinson+Disease&draw=2&rank=1.
451. Trial.gov, C. *Safety Evaluation of Cellavita HD Administered Intravenously in Participants With Huntington's Disease (SAVE-DH).* 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT02728115?term=stem+cell&cond=Huntington+Disease&draw=2&rank=2.
452. Trial.gov, C. *CJD (Creutzfeldt-Jakob Disease) Quinacrine Study.* 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT00183092?cond=Prion+Diseases&draw=2&rank=5.
453. Trial.gov, C. *Human Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis (ALS) (hNSCALS).* 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT01640067?term=stem+cell&cond=Amyotrophic+lateral+sclerosis&draw=2&rank=5.
454. Trial.gov, C. *Neural Stem Cell Transplantation in Multiple Sclerosis Patients (STEMS).* 2020 [cited 2020 14th September 2020]; Available from: https://clinicaltrials.gov/ct2/show/NCT03269071?term=stem+cell&cond=Multiple+Sclerosis&draw=2&rank=3.

Figure 1

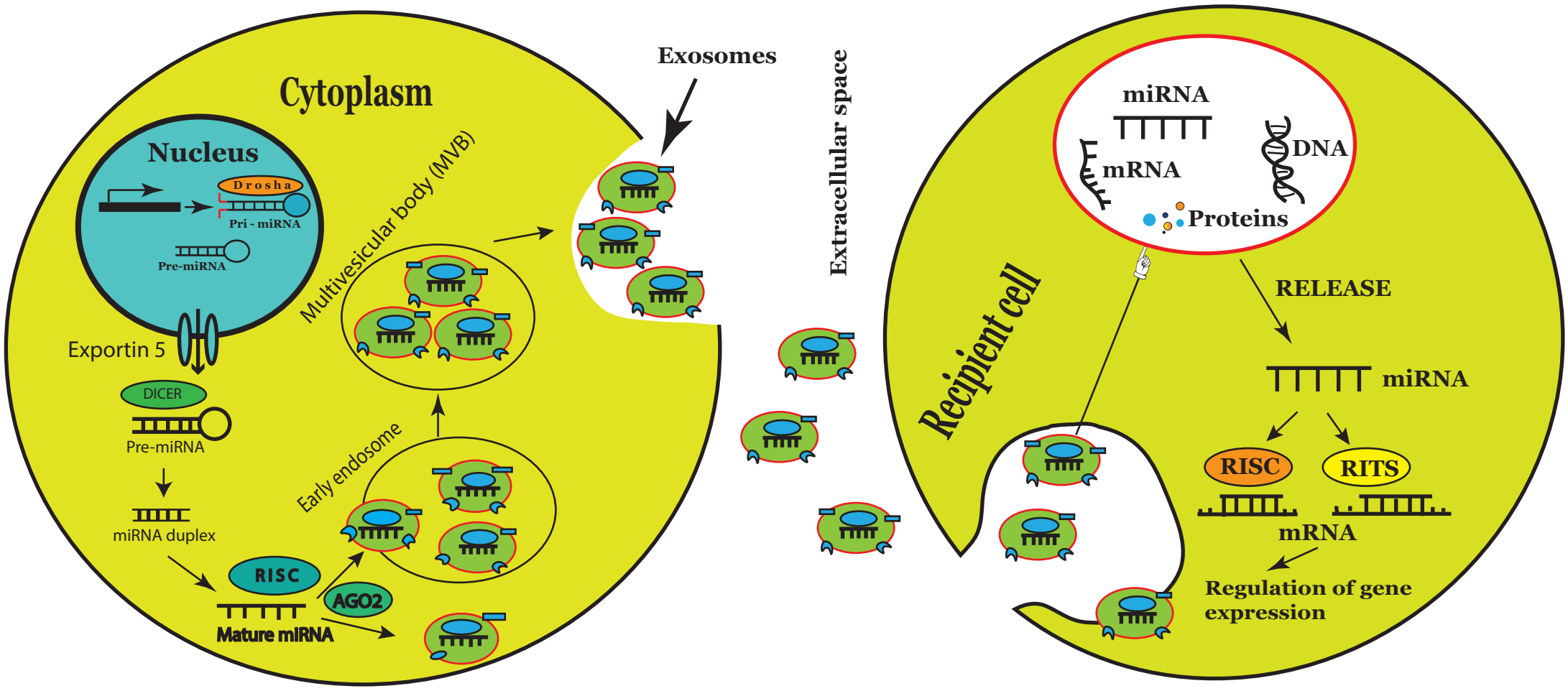
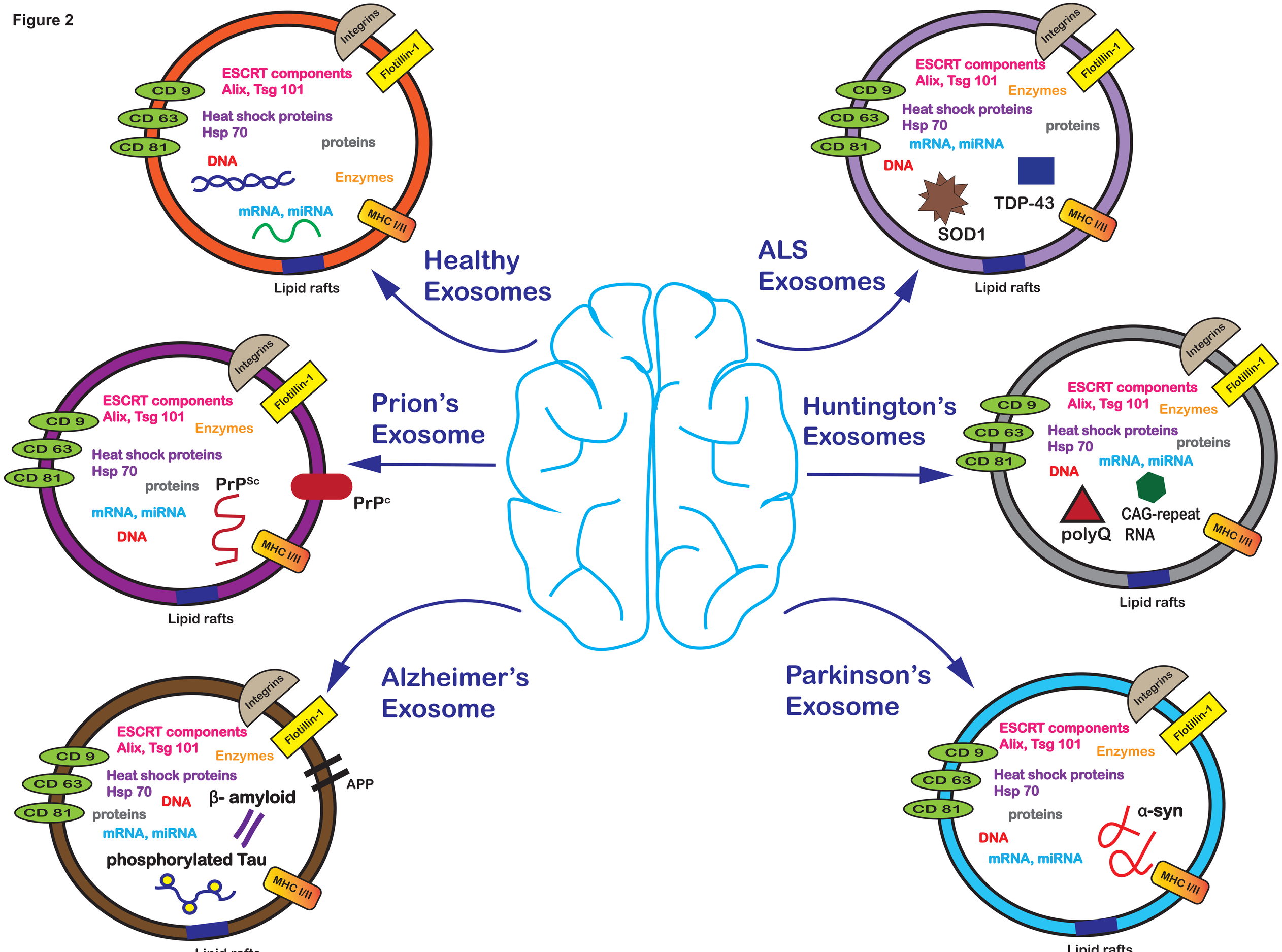

Cytoplasm
Nucleus
Drosha
Pri - miRNA
Pre-miRNA
Exportin 5
DICER
Pre-miRNA
miRNA duplex
RISC
AGO2
Mature miRNA
Multivesicular body (MVB)
Early endosome
Exosomes
Extracellular space
Recipient cell
miRNA
mRNA
DNA
Proteins
RELEASE
miRNA
RISC
RITS
mRNA
Regulation of gene expression

Figure 2


Integrins
Flotillin-1
CD 9
CD 63
CD 81
ESCRT components
Alix, Tsg 101
Heat shock proteins
Hsp 70
proteins
DNA
Enzymes
mRNA, miRNA
MHC I/II
Lipid rafts
Healthy
Exosomes
ALS
Exosomes
TDP-43
SOD1
Prion's
Exosome
PrPSc
PrPC
Huntington's
Exosomes
CAG-repeat
RNA
polyQ
Alzheimer's
Exosome
APP
β- amyloid
phosphorylated Tau
Parkinson's
Exosome
α-syn

	miRNA	Regulation	Region	Target	Reference
1	miR- 132	Downregulated	Brain tissue	p250GAP mRNA; PTBP2	[329-331]
2	miR-101	Downregulated	Brain Tissue	APP, Beclin1 and Atg4d	[110, 332]
3	miR-106b5p	Downregulated	Serum-AD patients	APP	[333, 334]
4	miR-135a	Downregulated	Serum Exosome_ AD Patients	BACE1, APP	[335, 336]
5	mir146a	Upregulated	Neocortical extracellular fluid (ECF) and in the cerebrospinal fluid (CSF)	APP/Tau; complement factor H (CFH)	[337-339]
6	miR-153	Downregulated	Brain Tissue	APP	[340, 341]
7	miR-155	Upregulated	Neocortical extracellular fluid (ECF) and in the cerebrospinal fluid (CSF)	APP/Tau; complement factor H (CFH)	[337, 338, 342]
8	miR-16	Downregulated	Brain Tissue	APP	[343]
9	miR-17-5p	Downregulated	Brain Tissue	APP	[344]
10	miR-20a	Downregulated	Brain Tissue	APP	[344, 345]
11	miR-644	Downregulated	Cultured Neuronal Cells	APP	[345]
12	miR-655	Downregulated	Cultured Neuronal Cells	APP	[345]
13	miR-9	Downregulated	AD- hippocampus and medial frontal gyrus, Serum_ AD Patients	TGFBI, SYNJ1, SYNPR, GMEB2, p250GAP mRNA, SPT, APP	[329, 346, 347]
14	miR-298	downregulated	Cultured Neuronal Cells	BACE1	[333, 348, 349]
15	miR-328	downregulated	Serum- AD Patients	BACE1	[333, 348, 349]
16	miR-423	Upregulated	Hippocampus_ Human	IDH2	[329]
17	miR-98	Downregulated	Cerebellum_ Human	IDH2	[329]
18	miR-125b	Down regulated	Serum_ AD Patients	CDKN2, SYN-2, 15-LOX	[346]
19	miR-181	Down regulated	Serum_ AD Patients	BTBD3, TRIM, SIRT1	[346]
20	miR-146b	Downregulated	Hippocampus_ Human	TLR signaling	[350]
21	miR-107	Down regulated	AD Brain	BACE1	[110]
22	miR-124	upregulated	AD Brain	PTPN1, BACE1	[332, 351, 352]
23	miR-195	Upregulated	AD Brain	ApoE/PPI Pathway	[353]
24	miR-29 (a/b)	Downregulated	AD Brain	BACE1, APP	[333, 354]
25	miR-34	Upregulated	Brain Tissue	SYT1, SNAP25, STX1A, SNAP25, and UNC 13B	[355]
26	miR-200b	Downregulated	CSF_ AD Patients	BACE1, APP	[335, 356]
27	mir-429	Downregulated	CSF_ AD Patients	BACE1, APP	[335, 357]
28	mir-384	Downregulated	Serum_Exosome_ AD Patients	BACE1, APP	[336]

Table 1 Alzheimer's disease Micro RNAs and possible targets

	miRNA	Regulation	Region	Target	Reference
1	miR-106a	Upregulated	PD brain samples	HSC70	[358]
2	miR-16-1	Upregulation	Neuronal Cells	HSP70, α-SYN	[359]
3	miR-214	Downregulation	PD-SERUM	α-SYN	[360-363]
4	miR221	Upregulation	PD- anterior cingulate gyri	SNCA, PARK2	[364]
5	miR-26b	upregulated	PD brain samples	HSP70	[358]
6	miR-27	Upregulated	neuronal cells	ATP5G3	[365]
7	miR-29b	Upregulated	neuronal cells	HSC70	[358]
8	miR-301b	Upregulated	neuronal cells	HSC70	[358]
9	miR-34b/c	Downregulation	neuronal cells	α-SYN, PAKN, PARK7	[134, 366]
10	miR-7	Downregulation	neuronal cells	α-SYN, NLRP3, VDAC1,KEAP1, Bax, SIR2, RELA, GLUT3, NFκB	[366-369]
11	miR-153	Down regulation	neural tissue	SNCA	[362, 370]
12	miR-21	Upregulated	neuronal cells	LAMP2a	[358]
13	miR-224	Upregulated	neuronal cells	LAMP2a	[358]
14	miR-373	Upregulated	neuronal cells	LAMP2a	[358]
15	miR-379	Upregulated	neuronal cells	LAMP2a	[358]
16	miR-128	Upregulated	brain tissue	TFEB	[371]
17	miR- 155	Upregulated	Neuronal Cells	ATP5G3	[365]
18	miR-494	Upregulated	Mice brain tissues	PARK7	[372]
20	miR-205	Down regulation	PD-frontal cortex	PARK8 (LRRK2)	[373]
21	miR-138-2-3p	rs66737902 T sequence binding	PD-Brain	PARK8 (LRRK2)	[374]
22	miR-144	upregulated	PD- anterior cingulate gyri	LRRK2, DRAM	[364]
23	miR-488	upregulated	PD- anterior cingulate gyri	PARK2, MTFMT	[364]
24	miR-199b	upregulated	PD- anterior cingulate gyri	ZNF440	[364]
25	miR-544a	upregulated	PD- anterior cingulate gyri	XIRP2	[364]

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

	miRNA	Regulation	Region	Target	Reference
1	miR-34	Upregulated	Brain	TREM2	[410, 411]
2	MiR-342-3p	upregulated	CJD brain	E2F1	[412-415]
3	miR-146a	upregulated	CJD Brain	TLR/IL1-R, CFH, IRAK-1	[416, 417]
4	miR-139-5p	upregulated	MicroGlial Cells	ROCK2	[412, 418]
5	miR-320	upregulated	Mouse Brain	MAPK1/ERK2 and MAPK3/ERK1	[412, 419-421]
6	miR-128	upregulated	Mouse Brain	DCX	[412, 422, 423]
7	miR-328	upregulated	Mouse Brain	PLCE1	[412, 424]
8	miR-26a-5p	upregulated	CJD Brain	ULK1	[425-427]
9	miR-16	Upregulation	Mouse brain	Neurotrophin receptor-mediated MAPK/ERK pathway	[428]
10	hsa-miR-93-5p	down regulation	CJD-Blood samples	IL-8, VEGF	[429-431]

Table 3 Prion Disease Micro RNAs and possible targets

	miRNA	Regulation	Region	target	Reference
1	miR-22	Downregulated	HD-Brain	HDAC4, REST, Rgs2	[432, 433]
2	miR-132	Downregulated	HD- Cortices	p250GAP, MeCP2, REST, Ago2	[330, 434]
3	miR-124	Downregulated	HD-Brain	SOX9, PTB1, PGC1	[435, 436]
4	miR-196a	Upregulated	HD-Prefrontal Cortex	Mutant HTT, ANX1A, BDNF	[437-439]
5	miR-10b-5p	Upregulated	HD-Prefrontal Cortex	Mutant HTT, BDNF, CREB1	[272, 440-442]
6	miR-146a	Upregulated	HD-Brain	HTT, TBP	[443-445]
7	miR-214	upregulated	STHdhQ111/HdhQ111 cells.	HTT	[446, 447]
8	miR-150	upregulated	STHdhQ111/HdhQ111 cells.	HTT, Rgs8, VEGF-A	[446]
9	miR-146a	upregulated	STHdhQ111/HdhQ111 cells.	HTT	[446]
10	miR-125b	upregulated	STHdhQ111/HdhQ111 cells.	HTT	[446]
11	miR-10b-5p	Upregulated	HD-Brain	BDNF	[448]
12	miR-128	Down regulated	HD Monkey--Brain	g HIP-1, HTT and SP-1	[185]
13	miR-9	Down regulated	HD peripheral leukocytes	Foxg1	[184]

Table 4 Huntington's Disease Micro RNAs and possible targets

	miRNA	Regulation	Region	target	Reference
1	miR-155	Upregulated	human ALS Cells	SOD1	[214]
2	miR-132-3p	Downregulated	CSF	43TARDBP, FUS and C9ORF72	[375]
3	miR-132-5p	Downregulated	CSF	43TARDBP, FUS and C9ORF72	[375]
4	let-7a-5p	Downregulated	CSF	HMGA1, MYO1F, PKM, RAB40C	[376, 377]
5	miR-128-3p	Downregulated	AL-Muscle Tissue	ABCG1, BAX, CTDSP1, LGALS3	[378, 379]
6	miR-130b-3p	Downregulated	CSF	SNAI3	[377]
7	miR-148a-3p	Downregulated	CSF	BAX, ITGA5	[376, 380]
8	miR-15a-5p	Downregulated	Peripheral Blood	HMGA1, UCP2	[381, 382]
9	miR-151a-5p	Downregulated	Peripheral Blood	ARHGDIA, OTUB1	[382]
10	miR-16-5p	Downregulated	Peripheral Blood	ARHGDIA, HDGF, HMGA1, ZYX	[376, 382]
11	miR-182-5p	Downregulated	Peripheral Blood	FLOT1, NFKBIB, PFN1, SMARCD3	[380, 382, 383]
12	miR-183-5p	Downregulated	Peripheral Blood	PTPA	[380, 382]
13	miR-186-5p	Downregulated	Peripheral Blood	PTTG1	[382, 384]
14	miR-22-3p	Downregulated	Peripheral Blood	BSG, CD151, LGALS9, PTMS	[376, 378, 382]
15	miR-221-3p	Downregulated	Peripheral Blood	BBC3, GRB10	[377, 380, 382, 385]
16	miR-223-3p	Downregulated	Peripheral Blood	HAX1, MYL9	[382, 386]
17	miR-23a-3p	Downregulated	Peripheral Blood	MT2A	[382, 385, 386]
18	miR-26a-5p	Downregulated	Peripheral Blood	HMGA1, ITGA5, PHB, PRKCD	[376-378, 382, 385]
19	miR-26b-5p	Downregulated	Peripheral Blood	MIEN1, MT-CO2	[382, 387]
20	miR-27b-3p	Downregulated	Peripheral Blood	PHB, PINK1	[376, 382, 388]
21	miR-30c-5p	Downregulated	Peripheral Blood	IER2, VIM	[382, 384]
22	miR-425-5p	Downregulated	Peripheral Blood	TACC3	[382, 389]
23	miR-451a	Downregulated	Peripheral Blood	CDKN2D	[377, 382, 386]
24	miR-550a-3p	Downregulated	Peripheral Blood	MAPK3	[379, 382]
25	miR-93-5p	Downregulated	Peripheral Blood	RHOC	[382, 388]

Table 5 Amyotrophic lateral sclerosis-Micro RNAs and possible targets

miRNA	Regulation	Region	Target	Reference
miR-146a	upregulated	CSF	IRAK-1, IRAK-2, TRAF6, CFH	[390, 391]
miR-150	upregulated	MS serum and CSF	Myb, AID, BACH1, CEBPB, CSFR	[255, 392]
miR-155	upregulated	Serum	cMAF, FADD, IKK, JARID2, PU.1, Ripk1, SOCS1, tab2, ARK1C1, ARK1C2	[391, 393]
miR-342-3p	downregulated	MS-Brain Tissue	AKR1C2	[393]
miR-183	upregulated	MS-Brain Tissue	AKR1C1	[393]
miR-320a	downregulated	MS-PBMC	MMP-9	[394]
miR-30b-5p	downregulated	PRMS-Erythrocytes	PGC-1α	[395-397]
miR-301a	upregulated	RRMS-PBMC	PIAS3, NKRF	[398]
miR-15a	upregulated	MS-PBMC	BCL2	[394]
miR-16-1	upregulated	MS-Blood Samples	BCL2	[394, 399]
miR-23a	Downregulated	MS-Serum Samples and Brain lesions	Myocyte enhancer factor-2	[400, 401]
miR-223	Downregulated	MS-Serum Samples and Brain lesions	Myocyte enhancer factor-2	[400, 401]
miR-27	Downregulated	MS Brain Lesions	Myocyte enhancer factor-2	[401]
miR-155-3p	upregulated	CD4+ Tcells	Dnaja2 and Dnajb1, HSP40	[402]
MiR-19b	Downregulated	CD4+ Tcells	PTEN	[403]
miR-17	Downregulated	CD4+ Tcells	Ikaros family zinc finger 4	[403]
miR-183C	upregulated	Th17 Cells	FOXO1	[404]
miR-96	upregulated	Th17 Cells	Il23r, Tbx21 and Ifng	[404]
miR-132	upregulated	EAE Mice	IL-17, IFN-γ	[405]
miR-125a-5p	upregulated	MS-Blood Samples	DIP2A, E2F2, ADD2	[383, 406]
miR-185-5p	upregulated	MS-Blood Samples	BACH2, GPX3	[383]
miR-25-3p	upregulated	MS-Blood Samples	ABCA1	[383, 407]
miR-148b-3p	Downregulated	MS-Blood Samples	TMED7	[383, 408, 409]

Table 6 Multiple Sclerosis Micro RNAs and possible targets

Table 7 – Characteristics of miRNAs binding sites in CDS mRNA genes with nucleotide repeats

Genes	miRNA	The beginning of binding site	Free energy change (ΔG, kJ/mole	The ΔG/ΔGm values (%)	Schemes of miRNA binding with mRNA genes
ATXN7	miR-1181	593	-112	88	5′ – CGCCGCG**CGGCGGCGGCGGCGG** – 3′ ||	|| |||||||||||||| 3′ – GCCGAGC-CCACCGCCGCUGCC – 5′
ZIC2	miR-1908-3p	1787	-116	88	5′ – **CGGCGGCGG**GG**CGG**G**CGGCGG**G – 3′ ||| |||||||| |||||| || 3′ – GCC-CCGCCUCGGCCGCCGGCC – 5′

Table 8 Current stem cell development

Disease	Therapy	Phase	Reference
Alzheimer's disease	Exosomes Derived from Allogenic Adipose Mesenchymal Stem Cells（MSCs-Exos）	I/II	[449]
Parkinson's Disease	The Effect of Adrenergic Blocker Therapy on Cardiac and Striatal Transporter Uptake in Pre-Motor and Symptomatic Parkinson's Disease	II	[450]
Huntington Disease	Cellavita HD is a stem-cell therapy	I	[451]
Prion diseases	Effectiveness of the medication quinacrine on survival in sporadic Creutzfeldt-Jakob disease (sCJD)	II	[452]
Amyotrophic Lateral Sclerosis	Intra-spinal Cord Delivery of Human Neural Stem Cells	I	[453]
Multiple Sclerosis	Neural Stem Cell Transplantation	I	[454]