Review

MicroRNAs (miRNAs) as Biomarkers for Diagnosis, Prognosis, or as Therapeutics Molecules in Neurodegenerative Diseases

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Review

MicroRNAs (miRNAs) as Biomarkers for Diagnosis, Prognosis, or as Therapeutics Molecules in Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases that include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS), arise due to numerous causes like protein accumulation and autoimmunity, characterized by neurologic depletion which lead to incapacity in normal physiological function such as thinking and movement in these patients. Glial cells perform a critical role in protective neuronal function; in the case of neuroinflammation, glial cell dysfunction can promote the development of neurodegenerative diseases. MiRNA participates in gene regulation and plays a vital role in many biological processes in the body; in the central nervous system (CNS), it can play an essential part in neural maturation and differentiation. In neurodegenerative diseases, miRNA dysregulation occurs, enhancing the development of these diseases. In this review, we discuss neurodegenerative diseases (Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)) and how miRNA is preserved as a diagnostic biomarker or therapeutic agent in these disorders. Finally, we highlighted miRNA as therapy.

Keywords: microglia cell ; neurodegenerative disease; miRNA; protein accumulation

Introduction

Neurodegenerative disease is a collective neurological disorder characterized by neuronal degradation that ultimately leads to cognitive and movement disability, includes Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD) and multiple sclerosis (MS) [1,2]. According to the World Health Organization, this disorder could become the second deadliest disease after cancer in the next fifteen years [3]. nervous system is nearly non- regenerative ,thus ; the development of these diseases are permanent[4].

Glial cells, which include microglia, astrocyte, and oligodendrocyte, play a significant role in protective neuronal function and regulation[5]. In neurodegenerative disease, Progression of the neuroinflammatory process occurs predominantly through microglia and astrocyte activation [6].

Neuroinflammation plays an active role in the pathogenesis of different neurodegenerative diseases [7], and microglia activation is a key factor in neuroinflamation[8]. microglia resident macrophage in brain[9] can act as either M1(pro-inflammatory) or M2 (anti-inflammatory) [10]. In the case of neuron impairment, this leads to microglia activation and the release of inflammatory cytokines to improve neuronal damage [11]. However, a neurodegenerative disorder characterized by persistent chronic inflammation will further activate microglia, which indicates more damage to

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neurons [9], through secreting various inflammatory and cytokine mediators [12]. (Figure 1). CX3CR1 receptor is found on the surface of different cells, including microglial cells [13], that interact with CX3CL1,[14] that found on neurons within globus pallidus, thalamus, striatum, [15], CX3CR1/CX3CL1 which acts as in different biological phenomena in CNS through regulating interaction between microglia, neurons, and immune cell, and participates in different cases of neuropathologies [14].

Astroceyt is one of the glial cells that are abundant in CNS and participate in metabolic supplement for neurons and participate in adjacent cell protection through liberating important chemical messengers such as growth factors, glutamine, lactic acid, and elimination of K+ and increased glutamate[16]. The metabolic exchange between astrocytes, microglia, and neurons mediates chronic inflammation and oxidative stress, leading to neurodegenerative disease progression[16,17].

The essential purpose of oligodendrocytes is myelin generation, and they provide support for neurons and prevent cell death via stimulating myelin recovery[18,19]. Chronic demyelination, such as in (MS) leads to myelin loss due to different pathological mechanisms such as loss of function of oligodendrocyte and mitochondrial dysfunction, oxidative stress enhancement, and at last lead to neuronal cell death. [20].

Early diagnosis of neurodegenerative disease can be helpful in disease treatment and elimination of its possible consequences. Thus one of the biomarkers reliable for this purpose is miRNA [21]

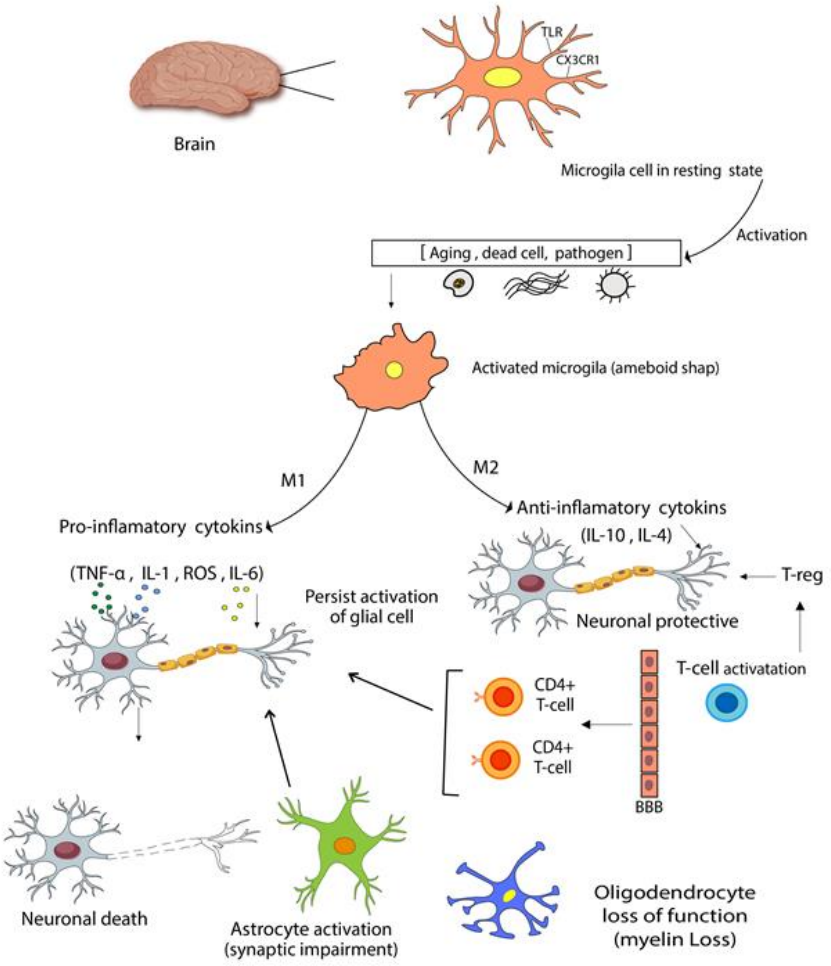

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Figure 1. Microglia and principle activation in the brain. Microglia normally present in a resting state that contains toll-like receptor (TLR) and CX3CR1, and due to activation such as in case of ageing, pathogen, and depression of dead cell lead to activation of microglia through TLR and CX3CR1; to become either (M1) that secreted proinflammatory cytokine-like tumor necrotic factor-α (TNF-α), interleukin-6 (IL-6) , reactive oxygen species (ROS) , or (M2) that secreted anti-inflammatory cytokine that have protect effect for example (IL-4, IL-10). In case of persist activation of microglia, this enhancing the persistent secretion of the pro-inflammatory cytokine, increased T-cell activation, which in turn activation of microglia that will affect astrocyte activation and loss of oligodendrocyte function; all this contributes to the neuronal death. This Fig was created by using (Adobe Illustrator 2020).

MicroRNAs (miRNAs) which play a significant role in neurodegenerative disease through different physiological process, belongs to non-coding RNAs (ncRNA)[3], and one of the characteristics of ncRNA do not encode specific protein[22]. NcRNA that is present typically in (CNS) that participates in the development and pathogenesis of this system, can be classified as small ncRNA that includes transfer RNA (tRNA), microRNAs (miRNAs), short small interference RNAs(siRNAs), piwi-interacting RNAs (pi-RNA), and long non-coding RNAs that include natural antisense transcript (NATs) and long intragenic RNAs non-coding RNAs (linc RNAs)[23],

MicroRNA with lengths of 21-25 nucleotides plays a critical role in the performance of many diverse biological functions in the cells, such as cell development, stem cell differentiation, oxidative stress[24], and tumor genesis [25]. Several miRNAs circulate in the central nervous system and play an essential role in neural maturation, differentiation, and development [26,27].

miRNA are synthesis from double–strand primary miRNA (pri-miRNA) that is synthesized via RNA polymerase II [28] and undergo more processing in the nucleus to generate precursor miRNA(pre-miRNA) hairpins by Drosha (type III ribonuclease) and DiGeorge critical region 8 (DGCR8) (RNA binding protein) [29], [30]. Then pre-miRNA exists in the cytoplasm through the nuclear pore complex in compensation with exportin-5 (XPO5) and GTPase RanGTP to protect it from the degradation process that occurs through nuclease enzyme[31,32]. In the cytoplasm, Dicer (type III ribonuclease) leads to cleavage of pre-miRNA to form mature miRNA; this mature miRNA is loaded into Argonaute protein (Ago) into the RNA-induced silencing complex (RISC), then when binding to the target region on mRNA (3'UTR) lead to suppression this region.[33].in case of any defect occurs in these processes, it can participate in the development of neurodegenerative diseases [35], Figure 2 (c).

In neurodegenerative disease, miRNAs play a significant role in neuronal malfunction through an increased buildup of protein and peptides in the pathogenic form [35]. The dicer enzyme in the nucleus is essential in miRNA synthesis [36]. When knocked out of specific areas in the brain, this leads to removing the dicer enzyme, and specific miRNA will affect and not be made, thus leading to the manifestation of neurodegenerative disorders[37].

This study focuses on the role of miRNAs in participation as diagnostic or prognosis in AD, PD, MS, and ALS or as therapy; Finally, we discuss types of therapeutic miRNA overall.

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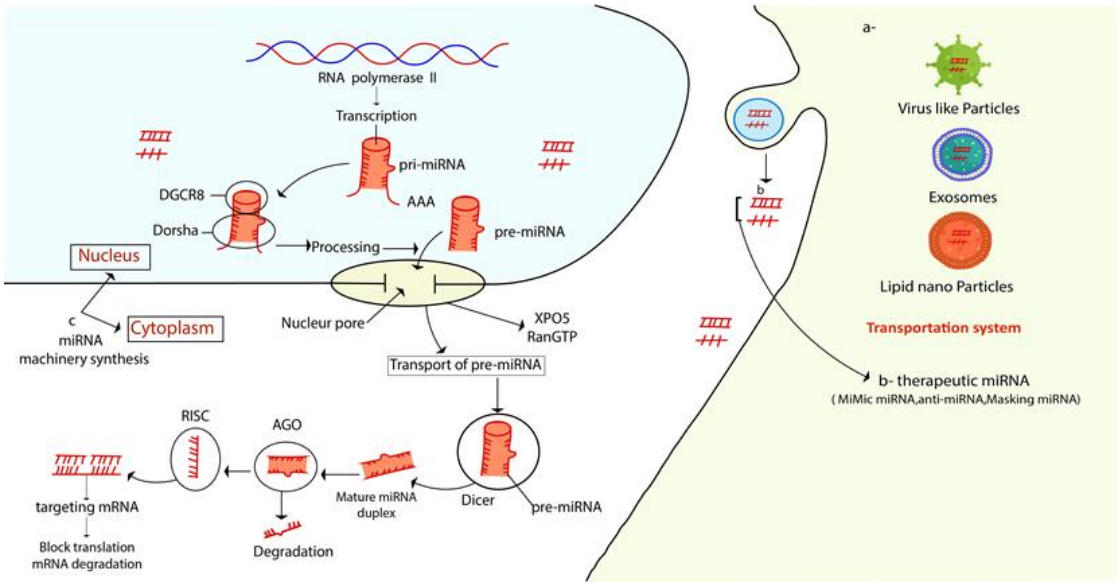

Figure 2. Schematic diagram of miRNA's transportation system, therapeutic, and machinery synthesis. (A) Showed transportation system, miRNA can be transported to cells inside the virus-like particles, lipid nanoparticles and exosomes. (B) Therapeutics miRNA can be a synthetic double or single strand that targets miRNA syntheses in the nucleus or cytoplasm, like (mimic miRNA, anti-miRNA, masking miRNA). (C) Synthesis of miRNA starts in the nucleus, pri-miRNA transcript from RNA polymerase II; after that, pre-miRNA formed through the processing of pri-miRNA by dorsha and DGCR8, pre-miRNA exported into the cytoplasm through nuclear pore in combination with XPO5, RanGTP, dicer lead to form mature miRNA in the cytoplasm, that mature miRNA loaded to (AGO), the unwanted stranded degraded, the functional strand loaded to RISC and lastly targeted complementary region 3' UTR on mRNA, which prompts mRNA degradation or block translation, this Fig. created by using (Adobe Illustrator 2020).

Role of miRNAs in neurodegenerative diseases.

Many mechanisms can facilitate damaging neurons and play a role in the development of different neurodegenerative diseases (Figure 3). In this section, we discuss AD, PD, MS and ALS and how can preserve miRNA in the neurodegenerative diseases as pathological biomarkers, diagnosis or therapy, Table 1.

Table 1. Some miRNA and their potential use in neurodegenerative diseases.

Type of Disease	Type of miRNA	Expression level	indication	reference
MS	Mir-193a	decreased	Prognostic, diagnostic marker, and act as therapeutic	[38]
MS	Let7b-5p, mir-143-3p	Decreased in CSF	Promising miRNA candidate to discriminate PPMS	[39]
MS	Mir-155a, mir-146a	Increased in level (serum)		[40]

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	Mir-34a, mir-143a,mir-373a	Decreased in level (serum)	Act as diagnostic, prognostic and therapeutic	
MS	Mir-10,mir-21,mir-124	Decreased (blood)	in the pathogenesis of MS	[41]
MS	MIR-146a	Decreased in whole blood and feces of RRMS in compression with CIS, decreased in female.	In fecal as Diagnostic, prognostic biomarker	[42]
PD	Mir -7-1-5p, mir-223-3p	Increased in serum and serum isolated exosome	play a role in inflammation in PD, a Potential biomarker to discriminate PD from HC	[43]
PD	MIR-24, MIR-195	Increased serum-EVs	Act as an active biomarker in the diagnosis of PD	[44]
	MIR-19b	Decreased Serum -EVs		
PD	MIR-22-3P	Decreased	As a diagnostic parameter in the early stage of PD	[45]
	22-3P, MIR-10b-5p,mir-151a-3p	increased (CSF)		
PD	Has-mir-144-3p	Decreased in serum	Play a role in the progression of the disease and as an Early marker of PD.	[46]
PD	Mir-27-a,	Increased plasma	Can act in early diagnosis of PD, Use of mir-27-a, mir 27-b as a potential therapeutic target	[47], [48]
	Mir-142-3p, mir-222,let-7a,let-7f	Decreased (plasma)		
PD	Mir-132	Increased(in males than in females) in prephrial blood	Biomarker for PD as diagnostic and disease progression	[49]
ALS	miR-16-5p	increased in plasma, CSF	Neuroprotective role in ALS after administration	[50]

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	mir-206	Increased plasma	of intrathecal linage negative cell,	
ALS	miR-23a	Increase in skeletal muscle in ALS patients and mouse model	Therapeutic inhibition of mir-23a may be a strategy to rescue peroxisome proliferator-activated receptor-γ coactivator (PGC-1α)activity and ameliorate skeletal muscle mitochondrial function in ALS, and down-regulation of miR-23a-3p has been proven to alleviate neuronal cell death and ROS	[51], [52]
ALS	Hsa-mir-4649-5p	Increased (plasma)	Acts as diagnostic markers	[53]
	Has-mir-4299	Decreased (plasma)		
AD	MIR-155,mir-146a, mir-125b ,mir-9,mir-34a	Upregulation Brain tissue of AD, ECF and CSF	Biomarker for AD	[54], [55]
AD	Mir-455-3p	Increased levels in blood serum, CSF post-mortem brain tissues, AD fibroblasts, AD β-lymphocytes, AD cell lines, transgenic AD (TgAD) mouse models and AD CSF	Biomarker and therapeutic	[56,57]
AD	Mir146a-5p	Upregulated in AD brain, neocortex and hippocampus	Act as Pathogenesis and therapeutic biomarker	[58,59]
AD	Mir-125b	Upregulated in AD brain tissue	Pathological role can be used as treating therapy by using anti-mir 125b, anti-NF-kB	[60]

Table 1 Abbreviations: AD, Alzheimer`s disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; MS, multiple sclerosis, PPMS; primary progressive multiple sclerosis; CIS, clinically isolated syndrome; ROS;

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reactive oxygen species , NF-KB, nuclear factor-kappa B; EVs , extravascular vesicle; HC, healthy control; CSF, cerebrospinal fluid. .

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most common prevalent neurodegenerative disease affecting aged people[61], and development as mental decline lead to memory problem and difficulty in language and social communication [62] [63].

AD occurs due to the accumulation of (amyloid β-peptide)Aβ plaques extracellular in the post-mortem, and neurofibrillary tangles (NFTs) that(composed from abnormal hyperphosphorylated tau-protein) as intracellular [64]. Thus, these triggers lead to changing occurs in synapses and synaptic plasticity in different parts of the brain, such as the neocortex, hippocampus, and limbic system, and lead to cognitive impairment in these patients with AD [65,66], [67].

Many other proteins can participate in the pathological of AD, such as cytoplasmic inclusion of TDP-43 accumulation in different parts of the brain hippocampus, amygdala, frontal neocortex, and entorhinal cortex/ inferior temporal cortex[68] and nuclear protein impairments hnRNP A1 and A2/B1 due to neurotoxin –mediated cholinergic impairments, could be lead to defective in processing of miRNA that contribute to pathogenesis and disease development [34,69].

Many investigators informed the role of miRNA in different diseases, such as AD [70], that showed miR-133b could be a promising biomarker for AD patients. Others published that miR-29,miR-181, and miR-9 play a significant role in immune response and inflammation in AD.[71]

There was noticed when overexpression of miR-455-3P in patients with AD this play as a pathological role in AD and can be used as a peripheral biomarker[72]. When Mir-125b overexpression in the brain frontal cortex of AD patients, this accelerated hyperphosphorylation of tau protein brain mice led to memory and learning skills impairments [73] and reported that miR-28-3P, miR-125b, and miR-9 might consider as prospective indicators for AD[74]. As explained previously, Aβ plaques accumulation in the brain, they have found numbers of miRNAs participate in the regulation of Aβ levels, as mir-15 plays a significant role in the regulation of BCL2 [75], while miR-34 downregulates BCL2 translation. BCL2 was associated with AD[76] when increased in a level reduced cognitive impairment progression and Aβ plaques in the AD of mouse model [77]. Mir 106 can be targeted as therapy in AD due to its ability to inhibit phosphorylation of tau protein through inhibition of Aβ1-42 at Tyr18[78]; therefore, when directing this pathway that participated in the pathogenesis of AD, through this miRNA can resort to the function the cell of the brain.

miRNAs can play an essential role in BACE-1 regulation[79] that act as β-secrets 1 that proteolysis of amyloid precursor protein (APP) to liberated Aβ peptide [80], through increasing or decreasing levels of BACE-1 [79], one of these miRNAs, is mir 149 was noted decreased in expression in serum of AD patients and can prospective diagnostic biomarker for AD, in case of overexpression could suppress Aβ accumulation through targeting BACE-1 in AD model cells and improving neuronal viability and can target as therapy for this disease [81].

Parkinson's disease (PD)

It is a disease that belongs to neurodegenerative disorders, affecting people with age over 65 years [82]. Arise from losing of dopamine neurons in the brain; this dopamine can act as a neurotransmitter, and due to this depletion, leads to movement slowing and reduced balance [83], furthermore was noted formation of inclusions of Lewy and Lewy neuritis bodies in the cytoplasm of a neuronal cell that mainly involved synuclein alpha protein (α-syn) [84]. Less than 20% account for a genetic mutation that participates in PD development that includes Parkin (PARK2), Parkinsonism-associated deglaze (DJ-1), α-synuclein (SNCA), and leucine-rich repeat kinase 2 (LRRK2)[85].

PD can advance as pathological and nonpathological progression as non–motor indications can be noted, such as constipation, sleep disorders, and depression[86].

Due to miRNAs play an essential role in biological cellular functions [87]; therefore, they can act as a biomarker in the identification of PD; one of these miRNAs is mir 132; in one study that showed

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overexpression of miR-132 in plasma samples in males with PD than females in compression to control, and established a potential role of mir 132 in the regulation of Nurr1 protein that participate in dopamine regulation[49]. Other miRNAs contributing to the rule of α-syn are miR-223 and miR-153, noted down-regulated in expression in serum, brain, and saliva of the PD mice model and thus can be considered a diagnostic biomarker in this disease [88]. Other published that miR-153 Increased in level from the extracted tissue of mouse brain and serum [89], [90], and was noted a negative correlation between miR-153 and nuclear factor-E2-related 2 (Nrf2) that participate in varied antioxidant genes transcription[91] when inhibited of miR-153 in MPP+ induced PD model, induced Nrf2 signalling pathway and preserve neuron from oxidative stress and can promote new strategy for therapy for PD [90].

Another indicated an increased level of mir 29a and mir 29c in the serum of females than males infected with PD; however, mir 29 significantly down-regulated in PD in comper healthy control, anyway needed further study to be indicated as a biomarker for PD [92].

Mir 375 upregulated in the human spinal motor neurons development and assisted spinal motor neurogenesis [93]; one study demonstrated that mir-375 overexpression improved dopaminergic neurons and inflammation by inhibition of specific protein-1 (SP-1)[94]; this protein act as a transcriptional factor, and when the elevated level in the brain lead to increased neuronal death [95].

miR-216a can inhibit the expression of Bax protein [96]. Bax protein belongs to the Bcl-2 gen family[97]; it acts in case of elevated level as prompter apoptosis and leads to cell death, and when decreased level, indicates inhibition of apoptosis [98]; thus, mir 216a and can potentially target in PD through regulation of Bax protein [96].

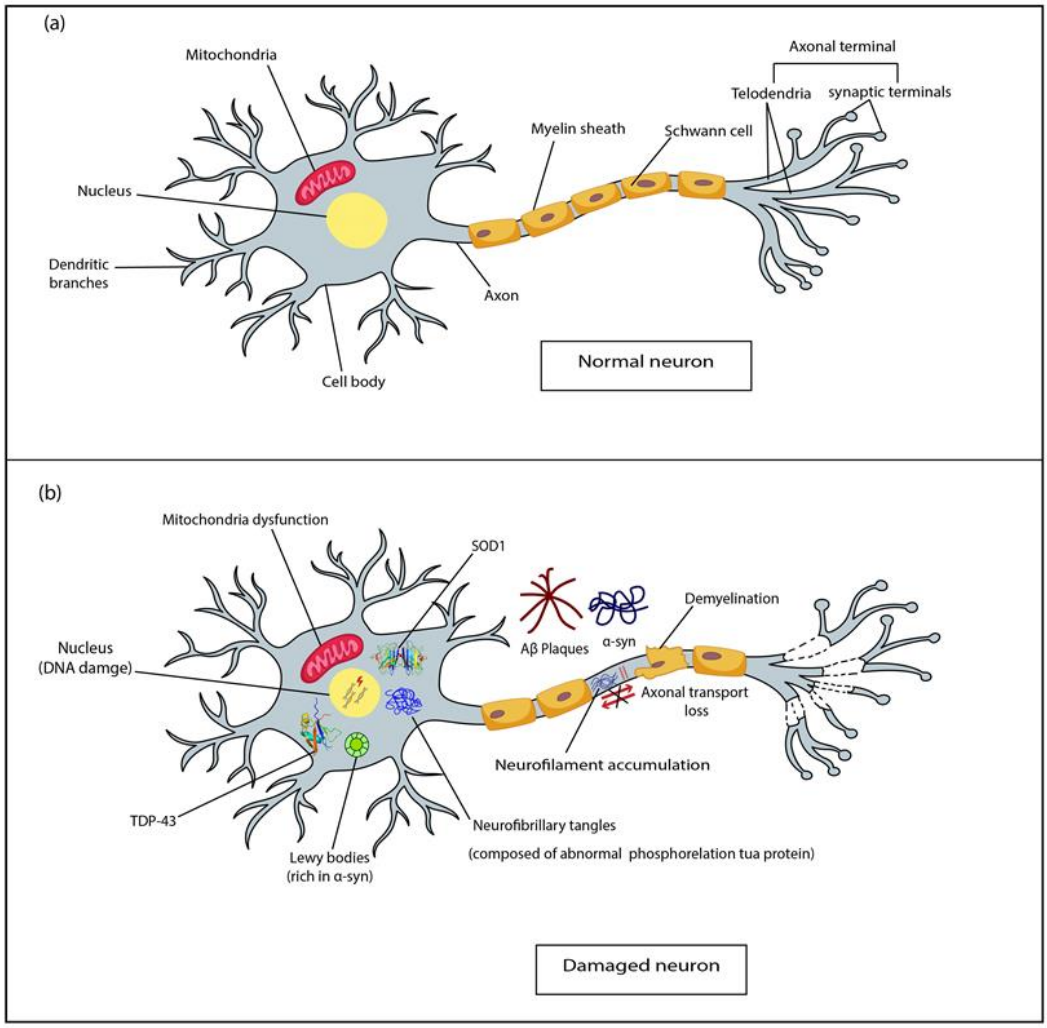

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Figure 3. Schematics overview of normal and damaging neurons. (A); showed normal constituents of neuron form cell body with usually present (nucleus, mitochondria,) to axon and how is generally warped in the myelin sheath, the axonal terminal that consists of normal function of telodendria and synaptic terminals, which ads in the neurotransmitter. (B) showed damaged neuron that occurs due to different mechanisms such as mitochondrial dysfunction, DNA damage, accumulation of different protein such as (TDP-43, Lewy body, Aβ plaques) in the cell body and around the neuronal cell, axonal transport loss such as (neurofilaments deposition, demyelination) which boost losing of the axonal terminal, all of these mechanisms participate in the loss of normal function of neurons, this Fig. created by using (Adobe Illustrator 2020).

Multiple sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune inflammatory disease characterized by demyelination of the myelin sheath of nerves in the spinal cord and brain; it is a disease of young adult onset[99]. Affecting females more than males [100]. Demyelination formation in white matter occurs due to increased infiltration of T-cells and the release of the cytokine in CNS, which will activate macrophage; this leads B-cells to transform into plasma cells and secreted autoantibodies which attack the myelin sheaths that surround the nerve fibres [101,102].

Many miRNAs have been identified in the different samples of MS patients; one of these, miR-922 and miR-181C in CSF [103], that's associated with transformation from clinically isolated syndrome (CIS) to relapsing-remitting MS (RRMS) characterized by deterioration that initiated via infiltration autoreactive immune cell in CNS [104], and the same association was noted in serum for miR-922 [103]. Mir-181c can control neuroinflammation by reducing microglial activation [105]and diminishing proinflammatory cytokines expressed through microglia [106]. Furthermore, it can indicate miR-181c as a biomarker in an increased inflammatory condition [107].

Mir-150 showed alteration in level in both plasma and CSF after treatment and was used as a biomarker for this disease [108]; mir-155 acts as a proinflammatory activator and plays an essential role in autoimmune diseases [109][110], such as MS pathogenesis; therefore, can be interpreted as one of the miRNAs that use in diagnosis in MS disease [111] Overexpression of miR-21, miR-146a/b in CSF of patients with MS with active lesions can give used as valuable markers in MS patients [112].

Another indicated that Mir-223 participated in remyelination and activation of M2 phagocyte, and in the case of knout mice, led to remyelination impairment [113]. Another study discussed when over-expression of mir-125a-3p contributed to the impairment of oligodendrocyte precursor cell (OPC) maturation, whereas inhibited expression stimulates this cell development [114]; thus, mir-125a-3p overexpression adds to the MS progression, which involvement repair impairment of demyelinated lesions [115].

ALS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of adult onset that is characterized by muscle paralysis that occurs due to advanced loss of upper and lower motor neurons ,and finally respiratory failure and death through the first five years of diagnosis[116], which can be either familial (fALS) that associated with high genetic adversity[117] or sporadic (sALS) that both environmental and genetic factors were involved in development [118].

The emergence of biomarkers for diagnosing ALS is needed; many studies showed the possible detection of miRNAs can help rapidly identify and observe ALS disease [119].

Many studies noted these miRNAs widely disrupted in skeletal muscle and brain and several biofluids in patients with ALS [120,121], such as mir 206, mir 124, mir 181, mir 155 [122–125]. One study showed that miR-27a-3p in the serum of ALS patients downregulated compared to controls and could indicate miR-27a-3p can serve as a diagnostic biomarker for ALS [126].

Many miRNAs participated in the pathogenesis of ALS; one of these was the downregulation of mir 218-2 due to processing defecting by dicer, which could affect neuronal robustness and, as a result, could be possible targeting therapy in diseases of motor neurons [127]. Fused in sarcoma (FUS)

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and Transactive response DNA binding protein-43 (TDP-43) that acts as a nuclear protein that participates in RNAs splicing and transcription initiation[128], in nucleus and cytoplasm through Drosha and Dicer, respectively [129], that was noted TDP-43 widely expressed in ALS cases[130]. At the same time, FUS is less common[131]. So, disturbance in these proteins associated with ALS can lead to dysregulation in the miRNA processing mechanism [132], which is one of the possible pathological involved in ALS disease.

A systematic review specified that serum miR-133b,miR-206, and miR-338-3p are prospective ALS markers[133], and miR-206 and miR-133, known as myomiRNA, are identified in skeletal muscle [134]. According to Pegoraro et al.'s study, mir-133 decreased in level in sALS patients, while miR-206 overexpression in muscle specimens in chromosome 9 open reading frame 72 (C9orf72) and superoxide dismutase 1(SOD1) mutations in ALS patients [135]. Mir1- act as muscle differential and Mir 133 act as muscle proliferation[135,136] , while mir-206 decelerates the progression of ALS disease via adding NM synapses regeneration[137]

mir 155 suggested a therapeutic element for treating ALS disease that acts as a proinflammatory activator when inhibited in ALS mice, improving disease progression [138]. Mir-146a, when down-regulated, can lead to malfunction of astrocytes and microglia and could contribute to the degeneration of motor neurons(MN); while upregulation provides a protective effect in ALS patients [139], it also leads to a level of NFL proteins decreased, and this maintenance of neuronal morphology[140].

miRNAs as therapy

One of the difficulties that prevent transfusion of miRNA is the blood-brain barrier (BBB) that prevents the miRNA from acting appropriately in brain tissues [33]; many promising transporting methods can improve this issue, such as using small extravascular vesicles (sEVs) [141], which can be administrated through intravenous injection [142], stereotactic injection, or nasally administrated,[143–145]. Another method of transportation is either a viral vector such as a recombinant adeno-associated virus or adeno-associated virus [146,147], or through a non-viral vector such as gold nanoparticles[148], and many others met such as hydrogel, Carbone-based nanoparticles like nano-diamonds, and smart mesoporous silica nanoparticles[149], [150,151], that facilities loading of miRNA in these system to specific site , Figure 2(a).

Several strategies have been developed to use miRNA as a therapeutic agent, such as mimic miRNA, by using synthetic double-strand miRNA, one as a guide and another as a passenger that is linked to another molecule, such as cholesterol, to enhance cellular uptake, lead to restoring of specific miRNA to an average level, that absent or downregulated during disease development and can improvement their specific target protein[152][153], or use (anti-miRNA) miRNA inhibitors, such as using synthetic oligonucleotides that are chemically modified, to target specific miRNA that is characterized in overexpression through targeting some pathway that involved in the miRNA biogenesis, at last, provided functions effectiveness, [154] [155][156].

Masking miRNA works to prevent inhibition mRNA from affecting endogenous miRNA [153,157], consisting of single-strand antisense oligonucleotides that interact with the binding site of miRNA in the 3'UTR of the target mRNA[158].

Another type was miRNA sponges that contain multiple binding sites to targeted miRNA that is separated by a few nucleotides, which is typically either viral vector or plasmid and introduced to gen through insertion into 3'UTR of selective gen that is driven by RNA polymerase II promoter [159], Figure 2(b).

There are some limitations of using miRNA as therapy, such as extracellular blockage in case of phagocytosis, degradation by nucleases enzyme, complement opsonization, or through intracellular blocking like non-specific site targeting ineffective cellular taking; regardless of this limitation, miRNA is still ideal targeting as a therapy due to safety, simplicity, effectiveness and easy contributed [160,161] and took multiple advantageous to the improvement of neurodegenerative disease consequences.

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Conclusion and future perspective

Recently increased evidence of neurodegenerative disease progression, which can affect aged people and young adults. Therefore, these diseases are a tremendous burden on the health organizations of each country, consequently needing emerging tools and biomarkers facilities in the early diagnosis and treatment to decrease the problem issues of these disorders. One of the promising molecules that add to the early diagnosis of this disease and identify possible pathological mechanisms that lead to the development of those disorders through increased or decreased expression, even if it can be used as therapy through many strategies that developed, is miRNAs. Despite related problems to blood-brain briar (BBB) that prevent the miRNA from acting appropriately in brain tissues, many promising transporting methods can improve this problem, such as viral vectors and non-viral vectors [162], [33]. So we need increasing investigation of brain-enriched miRNA due to plays a protective or inflammatory role, and by identifying novel pathways that participate in developing this neurodegenerative disease that can assist to considered miRNA-based therapy designed.

Abbreviations

AD, Alzheimer`s disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; HD, Huntington's disease; MS, multiple sclerosis; CX3CL1,fractalkine; miRNAs, MicroRNAs; nc-RNA, non-coding RNAs; pri-miRNA,primary miRNA; pre-miRNA, precursor miRNA; DGCR8, DiGeorge critical region 8;Ago,Argonaute;RISC,RNA-induced silencing complex; NF-KB, nuclear factor-kappa B; FUS, Fused in sarcoma;TDP-43,Transactive response DNA binding protein; C9orf72,chromosome 9 open reading frame 72; SOD1,superoxide dismutase 1; MN, motor neurons; MPP+, 1- mythel-4-phenylpyridinium; DA, dopamine; Aβ, amyloid β-peptide; NFTs, neurofibrillary tangles; CIS, clinically isolated syndrome; RRMS, relapsing remitting multiple sclerosis ; PPMS, primary progressive multiple sclerosis; sEVs , small extravascular vesicle; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator; ROS, reactive oxygen species; ECF, extracellular fluid ; HC, healthy control, ROS; reactive oxygen species.

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