miRNA in Nervous System

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microRNAs (miRNAs) are small single-stranded, non-coding RNAs that are 22–23 nucleotides in length. More than 2000 miRNA genes were identified. The last step in the processing of miRNAs is the Dicer-mediated cleavage. This final step is considered the interface link between miRNA and its regulators (e.g., E2 and androgens) on one hand and neurons on the other. Any disruption in the dicer-mediated cleavage of pre-miRNAs will affect mature miRNA production, which could propagate a negative effect on both cortical neurogenesis and the embryonic development of the nervous system. Several studies concluded that the disruption of mature miRNAs would probably affect the function of the nervous system by causing a reduction in neural progenitor cells' proliferation, a delay in the cell cycle, a disturbance in neural migration, an induction of apoptosis by activation of caspase 3, the stimulation of astrocyte differentiation, and the inhibition of neuronal differentiation.

miRNA-9 miRNA-29 regulation

1. miR-9 Activity and Regulation by Estrogens (Table 1)

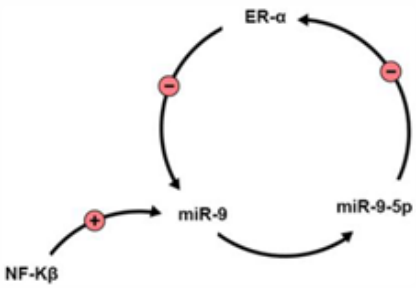
The activity of E2 and its action on miRNA are mainly mediated by the two ER subtypes (ERα, ERβ), both of which are expressed in the ventral hippocampus [1][2]. E2 participates in miRNA processing through ERα's interaction with the Dorsha complex. Many studies discussed the regulation of different miRNAs by steroid hormones. They showed that miR-9 expression could be regulated by E2. The availability of binding sites for ER within miR-9 promoters increases the possibility that E2 directly impacts miR-9 transcription [3].

In a study performed to assess the correlation between miR-9 and breast cancer progression, the authors observed high variability in miR-9 expression in human samples; this variability was strongly related to the expression of ERs, where ERα binds to Drosha during the maturation of miRNAs [4]. The ingenuity pathway analysis (IPA) further delineated a regulatory loop of miR-9-5p expression influenced by ERs [5][6][7].

The Nuclear Factor kappa-light-chain-enhancer of activated B-cells activates miR-9. Then, a negative feedback loop occurs where miR-9-5p directly targets the mRNA of ERα [3]. Another study assessed E2 regulation for miRNAs, especially in the brain. E2 played a critical role in expressing mature functional miRNA in the brain, which was age- and brain region-specific. The regulation of miR-9 expression by E2 exhibited similar age changes; the three-month-old rats showed that E2 reduces miR-9 expression levels in the dorsal hippocampus, with miR-9-3p expression increased in the same region. However, in rats aged 18 months or more, E2 continued reducing miR-9 expression, while the controlling effect of E2 on miR-9-3p could not be detected anymore [8].

Sirtuin 1 (SIRT1) is a protein deacetylase that has a role in aging, and is a target gene of E2 [9][10]. It partakes in many vital functions of the brain, such as energy balance, memory processing, and neuroprotection [11][12]. miR-9 expression is inversely correlated with that of SIRT1, in which the 3′ UTR region complements with the miR-9 sequence [13].

Table 1. Molecules interacting with miR-9 and estrogen.

Molecule	Interaction with miR-9	Reference
NF-Kβ		[3]
NEFH	miR-9 binds to the 3′UTR region of NEFH. miR-9-5p is significantly downregulated in ALS.	[14]
Serine Palmitoyltransferase [SPT]	SPT regulates Aβ in Alzheimer's disease, and is correlated with miR-9 serum and cortical levels.	[15]
SIRT1	Negative correlation with miR-9 levels. SIRT1 gene is a target of E2.	[9][10][11] [12][13]
E2	- Impacts expression via ERs on promotor regions or miR-9 and miR-9-5p. - Decreases miR-9 and increases miR-9-3p expression in dorsal hippocampus.	[5][6][7][8]
REST/CoREST	They regulate, and are regulated by miR-9. In HD, mutant huntingtin fails to regulate REST/CoREST, disrupting miR-9 activity.	[7][16][17]

le 2)

Principally, miRNAs have significant roles in gene expression regulation in different brain diseases and were suggested as therapeutic approaches in a wide range of human diseases because of their ability to deliver factors that would enhance repair mechanisms [18][19][20].

The miR-29 family is a group of miRNAs that is highly involved in developing mature and fully functional neurons. The miR-29 family consists of four transcripts; miR-29a, miR-29b-1, miR-29b-2 and miR-29c. Human miR-29a and

miR-29b-1 are transcribed from chromosome 7, while miR-29b-2 and miR-29c are transcribed from chromosome 1. Both miR-29b-1 and 2 have the same mature sequence [21].

The first of the three sequences in this group is miR-29a. It has been suggested that miR-29a can be of great importance in the process of neural maturation, based on the observed upregulation of miR-29a gene expression during the differentiation of neural stem cells (NSCs). Infecting the NSCs with lentiviral-mediated miR-29a was associated with a significant increase in microtubule-associated protein 2 positive neurons, as well as a significant reduction in astrocytes. This is mediated through targeting the phosphatase and tensin homolog, commonly known as PTEN, which plays a vital role in the differentiation and growth of NSCs, making its deletion an essential step in optimizing neural maturation [22][23][24][25].

Other direct targets for miR-29a have been proposed, such as the expression of the protein Doublecortin, which restricts axonal branching [26]. By inhibiting this protein when it is overly expressed in mice's cortical neurons, miR-29a increased the rates of axon branching in these cells [27]. Moreover, the widespread death of neurons was observed in mice following the knockdown of miR-29a using a chemically engineered oligonucleotide, i.e., locked nucleic acid antagomir (blockmir) called LNA29a/c. It is believed that the effect of miR-29a knockdown might be propagated through multiple mediators, like the voltage-dependent anion channel 1, a pro-apoptotic mediator that is inhibited by miR-29a [28][29]. miR-29b has been suggested as a rescue factor for neuronal cells, as it silences the pro-apoptotic BH3-only gene family [30]. In principle, miRNAs have significant roles in gene expression regulation in different brain diseases and were suggested as therapeutic approaches in a wide range of human diseases because of their ability to deliver factors that would enhance repair mechanisms.

The expression of miRNAs in embryonic and adult brains is controversial. It has been suggested that the miR-29 family is not expressed in the embryonic brain. However, further investigation showed that miR-29b is over-expressed in NSCs, and regulates embryonic proliferation and neurogenesis by targeting T-cell factor-mediated inhibitors, and the Wnt/β-catenin signaling pathway [31][32]. It was suggested that sex chromosomes might control miRNAs in neurodegenerative disorders [33][34]. In the brains of patients with neurological diseases such as Alzheimer's disease (AD) or schizophrenia, only a few human studies have assessed sex differences in miRNA expression [35][36].

Table 2. Molecules interacting with miR-29.

Molecule	Interaction with miR-29	Reference
Doublecortin	miR-29a targets doublecortin expression, reducing axonal branching	[26]
Voltage-dependent anion channel 1	miR-29a regulates this molecule, reducing apoptosis	[28][29]

Molecule	Interaction with miR-29	Reference
BH3-only family	miR-29b silences this proapoptotic gene family	[30]
Wnt/βcatenin signaling	miR-29b regulates this pathway, hereby affecting embryonic proliferation and neurogenesis	[31][32]
BACE	Negative correlation with miR-29a, miR-29b and miR-29c-3p expression in AD	[37]
DNA methyltransferase III beta (DNMT3B)	miR-29c acts on DNMT3B to reduce BDNF levels in AD invitro models.	[38]
Parkinsonism-associated Deglycase (PARK7)	miR-29 regulates this molecule. It is also regulated by estrogens and is implicated in PD pathology.	[39][40]
Bcl2L2	Bcl2L2 gene, which is antiapoptotic, is regulated by miR-29b.	[21][41][42] [43]

3. Alzheimer's Disease

The progression of AD is characterized by the accumulation of plaques made of short β-amyloid peptides. These peptides emerge from proteolytic cleavage of the β-amyloid precursor protein (APP) by a β-secretase known as the β-site APP-cleaving enzyme (BACE) [44][45]. It has been observed that miR-29a, miR-29b and miR-29c-3p have low expression levels in AD with abnormally high levels of BACE [37]. Despite the low expression levels, the miR-29 clad were found to be abnormally high in the CSF of two cohorts of AD patients [46][47], achieving 89% sensitivity and 70% specificity for the miR-29a [46], making it a potential candidate for future AD biomarker research [48]. However, some potentially contradicting evidence found low CSF miR-29c levels in AD patients. These were found to be linked to the decreased levels of BDNF expression, an effect that was posited to be mediated by DNA methyltransferase 3 through some in vitro experiments [38]. Besides, estrogens are essential in AD pathogenesis since they might decrease β-amyloid protein levels as a neuroprotective mechanism against the disease [36][49]. Pan and colleagues showed that estradiol's neuroprotective effect against amyloid pathology in AD is potentially mediated by the miR-106b-5p/TXNIP axis in a neuroblastoma cell line [50], while another study showed that estradiol treatment on ovarectomized AD model mice slowed the pathological conformational changes of tau. This change was potentiated by the decreased expression of miR-218 [51]. Sedghi et al. showed that when levels of miR-29a are raised it produces a neuroprotective effect in the peripheral blood mononuclear cells of AD patients [52]. While this effect was realized using klotho and linagliptin treatment on isolated cells, it paves the road for testing other interventions with similar effects on the implicated pathways.

4. Parkinson Disease

MiR-29a, miR-29b-1, and miR-29b-2 are over-expressed in the brains of Parkinson's disease (PD) patients [53], while miR-29b-2-5p was under-expressed in another study [54]. miR-29 has significant roles in PD pathology, such as apoptosis and neuronal survival, motor function tuning, the immune response (by regulating T1 helper cells), and genetic modulation [55][56]. Inhibiting miR-29 expression in the mouse brain caused massive rates of neuronal death, especially in the hippocampus and cerebellum [29]. miR-29 also targets Parkinsonism Associated Deglycase, which is thought to be regulated by androgens and estrogens [39][40]. It is believed that the role of miR-29 in the pathophysiology of PD needs further investigation in the clinical setting [55][57]. As for other miRNAs, Liu and colleagues used computational methods to study the differentially-expressed genes in PD patients. By constructing a miRNA-mRNA regulatory network, they found that has-miR-142 was the most vital miRNA in the network, carrying out its effects on GNAQ, TMTC2, KYNU, and BEND2 [58].

5. Huntington's Disease

Pre-clinical studies done on HD showed a consistent downregulation of miR-9 and miR-29; this effect was constant across different animal and animal cell models [59]. One of miR-9/9*'s functions is regulating the function of REST/CoREST in the cell. Because REST/CoREST targets miR-9/9* as well, and because mutant huntingtin in HD patients fails to regulate the levels of REST in the cell, levels of REST become unusually high in the neurons of HD patients. Ultimately, this leads to the misregulation of gene expression in those neurons [16][17]. Another study found that miR-9*, but not miR-9 or miR-29b, were significantly downregulated in the peripheral leukocytes of HD patients compared to controls [7]. However, the level of miR-9* was not correlated to the UHDRS score in HD patients.

6. Other Brain Diseases

Owing to their potent antifibrotic effect, miR-29s have been strongly linked to the pathophysiology and management of stroke. At the infarction region, miR-29b levels were notably lower than in other healthy brain areas. Studies showed significant improvement in patients' outcomes when utilizing a special approach to deliver a miR-29b mimic to combat the stroke-induced loss of miR-29b. It was also postulated that miR-29b levels were significantly increased during ischemic brain injuries. A recent study found that the overexpression of miR-29b reduced the neuronal cell death observed during brain ischemia. Conversely, the downregulation of miR-29b was accompanied by increased rates of neuronal cell death. It was proposed that miR-29b carries its action through inhibiting the expression of the antiapoptotic gene Bcl2L2. Therefore, when Bcl2L2 is overexpressed, it leads to increased neuronal cell survival [21][41][42][43].

The modulation of post-stroke-induced neurogenesis by miR-9, and Histone Deacetylase 4 was documented [60]. In brain neurogenic areas, miR-9 is widely expressed, which has ramifications for the differentiation of embryonic, and adult progenitor cells [61]. The effect of miR-9 in reducing neuronal apoptosis after ischemic stroke was investigated in a few studies [62][63]. Wei et al. found that miR-9 directly targets Bcl2l11, and that altering miR-9 causes changes

to Bcl2l11 protein levels [62]. The authors concluded that miR-9 targets Bcl2l11 to facilitate cell apoptosis. Another study showed that miR-9 upregulation promoted neuronal survival, and regeneration following ischemic stroke [64]. The authors put forth a key mechanism by which HDAC4 inactivation positively regulated the expression of miR-9 and ameliorated ischemic insult in vitro. This may contribute to overcoming the hurdles hampering the adoption of miRNA-based therapeutics for ischemic stroke. A recent study by Wang et al. showed that, compared to healthy people, early-stage acute ischemic stroke patients had higher blood levels of miR-9-5p. Serum levels of miR-9-5p were significantly correlated with patient prognosis, with high concentrations being linked to unfavorable patient outcomes [65].

In gliomas, Wu et al. documented that elevated miR-9 expression might be involved in tumour progression, and proposed miR-9 as a valuable marker to predict the clinical prognosis of glioma patients, particularly those with advanced subtypes [66]. Another study by Tan et al. [67] showed that miR-9 is substantially expressed in glioma cells. miR-9 suppressed glioma cell growth, and increased migration by directly targeting cAMP-response element binding protein as well as neurofibromin 1. Further studies also documented that miR-9 plays an important role in glioma pathogenesis, and might be used as a prognostic marker, and possible therapeutic target for gliomas [68][69]. On the other hand, miR-9 overexpression significantly inhibited the growth of U87 glioma cells. The growth limitation was primarily attributable to the stimulation of apoptosis, which coincided with an increase in the Bax/Bcl-2 ratio [70]. miR-9 overexpression caused cell cycle arrest in U87 glioma cells at the G2/M checkpoint, and miR-9 inhibited the migration as well as invasion of U87 glioma cells [70]. In their study, Shi et al. investigated miR-29s as a tumor suppressor in gliomas using 187 human glioma specimens as well as 20 nontumoral brain specimens. The authors documented that when glioma grade and the Ki-67 index rose, the expression of miR-29a/b/c substantially decreased [71]. This highlights the importance of miR-29a/b/c and TRAF4 in predicting prognosis and their possible therapeutic role in malignant gliomas.

Research has gradually moved away from safeguarding neurons and toward investigating the combined effects of the neurovascular unit on traumatic brain injury (TBI) in recent years as a result of the ongoing investigation of the pathological process [72][73][74]. This shift highlights the necessity of angiogenesis for neurological functional recovery after TBI. By triggering the Hedgehog pathway, and enhancing the p-AKT expression, Wu et al. documented that miR-9-5p stimulates angiogenesis in the injured cerebral cortex. This highlights the possibility that miR-9-5p may be a useful therapeutic target for TBI. Mu et al. provided a new function for miR-29a in controlling NSC development and neurite outgrowth. They also provided a potential theoretical base for how NSC migration contributes to brain growth as well as damage repair [75]. By inhibiting NLRP3 expression and activation, miR-29a-5p mimics have been documented to protect against TBI-induced enhanced endothelial cell permeability, and BBB dysfunction [76].

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