Emerging Role of microRNAs in Dementia

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Abstract

MicroRNAs are small non-coding RNAs regulating mRNA translation. They play a crucial role in regulating homeostasis in neurons, especially in regulating local and stimulation dependent protein synthesis. Since activity-mediated protein synthesis in neurons is critical for memory and cognition, microRNAs have become key players in modulating these processes. Dementia is a broad term used for symptoms involving decline of memory and cognition. Several studies have implicated the dysregulation of microRNAs in many brain diseases like neurodegenerative diseases, neurodevelopmental disorders, brain injuries and dementia. In this review, we give an overview of microRNA-mediated regulation of proteins and cellular processes affected in dementia pathology, hence illustrating the importance of microRNAs in normal functioning. We also focus on a relatively less explored area in dementia pathology—the importance of activity-mediated protein synthesis at the synapse and the role of microRNAs in modulating this. Overall, this review will be helpful in looking at the significance of microRNAs in dementia from the perspective of defective regulation of protein synthesis and synaptic dysfunction.

Introduction

Dementia is a general term used to describe the loss of memory and cognitive defects common to many neurological disorders. There are many different causes and types of dementia where Alzheimer's disease (AD), vascular dementia and fronto-temporal dementia (FTD) are among the most common [1–3]. Dementia is progressive and in most cases involves significant loss of neurons by the time the problem is diagnosed. Vascular dementia happens due to the loss of blood supply to specific regions of brain [1], and it is clearly distinct from the other major causes of dementia such as AD and FTD. In this review, we primarily focus on dementia resulting from AD and FTD. In AD and FTD, majority of the cases are sporadic (where the genetic cause is unknown), but still a large number of genes are identified whose mutations are either directly implicated in the pathology or considered to be risk factors [2,3]. In both sporadic and familial cases, molecular pathology has many common features such as increased oxidative stress, mitochondrial dysfunction, intracellular and extracellular protein/peptide aggregation and endoplasmic reticulum (ER) stress due to misfolded and aggregated proteins [4–8]. Synaptic dysfunction and defects in regulation of protein synthesis are interlinked factors that are likely to have significant impact on the pathology of AD and FTD [8–12] but are relatively less studied. In this article, we review recent work about the defective protein synthesis, particularly involving microRNAs contributing to the molecular pathology of dementia. We also discuss the emerging concepts about defective translation regulation as an important cause of synaptic dysfunction observed in dementia.

MicroRNAs, which were discovered only two decades ago, have attained a central position in our understanding of translation regulation. MicroRNAs are small (~20 nt) noncoding RNAs encoded as much longer precursors which are processed into

their mature form by different RNases. The primary transcript of miRNAs encoded by RNA polymerase II undergoes nuclear processing by Drosha and DGCR8 to form the precursor miRNA (pre-miRNA). The pre-miRNAs are loaded onto the complex of Dicer and Argonaute (AGO) for further processing into the single stranded mature miRNAs [13]. Dicer also associates with other proteins such as TAR RNA binding protein (TRBP) and protein kinase interferon-inducible double-stranded RNA-dependent activator (PACT) for more efficient processing of pre-miRNAs [14]. TRBP and PACT directly interact with protein kinase R (PKR) and hence also act as factors that link the miRNA processing to stress response [14].The mature miRNAs are recruited on their cognate target mRNAs (based on their "seed" sequence) along with Argonaute (Ago) protein. Argonaute then recruits several other proteins (such as GW182, FMRP and different de-capping and de-adenylating enzymes) and constitutes the microRNA-induced silencing complex (miRISC) [15,16]. MiRISC can inhibit translation and degrade the mRNA at different kinetics based on its composition and many other determinants. Formation of miRISC does not necessarily mean degradation of the mRNA since this inhibition can be often reversed and translation can resume. This is particularly relevant at the synapse where activity-mediated translation requires an efficient mechanism to reversibly inhibit protein synthesis [17,18].

Due to their key role in translation regulation, microRNAs are implicated in the pathology of many disorders from cancer to neurodegeneration. In dementia, most of the times, protein/peptide aggregation plays a causative role in the pathology. In such cases, translation regulation of proteins and enzymes that are involved in the generation and clearance of these peptides/aggregates is of critical importance. Several microRNAs are reported to be involved in this regulation and any change in their expression and function will have a significant impact on the pathology of dementia. Apart from this, microRNAs play a very important role in the regulation of many cellular organelles (such as mitochondria, ER) and processes (such as autophagy, calcium homeostasis, neurotransmitter homeostasis) which are affected in both familial and sporadic cases of dementia. More recently, the importance of microRNAs in synaptic function is illustrated by several reports. This should draw the attention of dementia researchers since synaptic dysfunction is the most common and important hall mark of cognitive loss in all cases of dementia irrespective of their origin.

In this review, we first discuss the role microRNAs in the translation regulation of many proteins directly implicated in the pathology of AD and FTD, which are major contributors to dementia. In the later section, we review the role microRNAs in regulating the important cellular organelles and processes which are implicated in neurodegeneration. We further review the role of microRNAs in synaptic translation, synaptic signaling and their implication to neurodegeneration, which is a frontier area for dementia research. Finally, we review the use of microRNAs as biomarkers for various forms of dementia and their potential use as therapeutic tools.

Role of MicroRNAs in Regulating the Proteins Directly Implicated in Dementia

In this section, we mainly focus on the proteins directly implicated in pathology of AD and FTD and their microRNA-mediated regulation. Many of these proteins are causative factors for the disease, while others are associated proteins acting as risk factors or protective agents. For each of these proteins, their expression and activity is reported to be regulated by several microRNAs. These microRNAs are likely to affect the disease pathology directly, and many of these microRNA levels are reported to be affected in dementia patients.

MicroRNAs regulating the proteins implicated in AD

AD is a progressive neurodegenerative disorder and a major leading cause for dementia. Clinically, AD is characterized by the presence of extracellular Aβ deposits and intracellular neurofibrillary tangles of hyperphosphorylated tau (MAPT) [2]. While majority of cases of AD are late-onset sporadic cases, about 5% cases are early onset and contributed by mutations in genes encoding specific proteins. Amyloid precursor protein (APP) is one of the primary proteins implicated in AD and is responsible for the generation of Aβ peptides. Although the exact function of APP in the cell is not well understood, it is shown to be important for neurite outgrowth and neuron motility [19]. APP is a transmembrane protein that is reported to be localized to the plasma membrane, ER, trans-Golgi network, endosomes and mitochondria. APP can undergo two different kinds of proteolytic cleavage pathways—the amyloidogenic pathway, which generates Aβ peptides (processed by β-secretase and ϒ-secretase), and the non-amyloidogenic pathway, which prevents Aβ generation (processed by α-secretase and ϒ-secretase) [20]. A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), a zinc metalloproteinase, is the principal constitutive α-secretase present in the neurons. With both APP and ADAM10 being localized to the plasma membrane, it is considered to be the main site of the α-cleavage [21]. The major β-secretase in the brain is reported to be BACE1, which is a

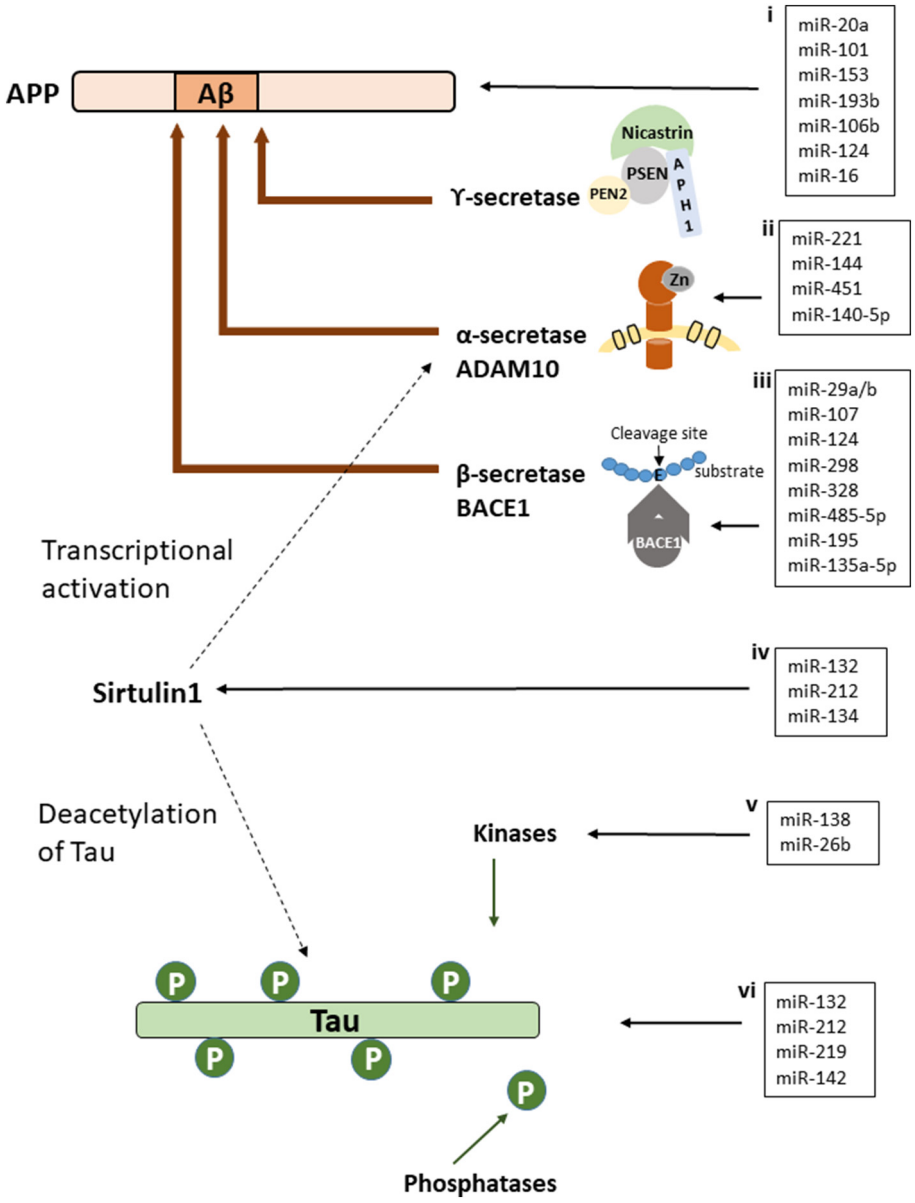

Fig. 1. MicroRNA-mediated regulation of proteins implicated in dementia pathology. MicroRNAs are involved in regulating the expression, splicing and post-translational modification of several proteins that are directly implicated in dementia pathology. This figure shows the microRNAs regulating the protein APP (i) along with its secretases ADAM10 (ii) and BACE1 (iii). MicroRNA-mediated regulation of tau expression (v) and its phosphorylation (vi) is also shown in the figure. Similarly, microRNAs regulating the expression of Sirtulin1 are also shown. Sirt1 is associated with dementia as it has roles in regulating both APP processing (through transcriptional activation of ADAM10) and tau pathology (through deacetylation of tau).

membrane-bound aspartyl protease. The main site of β-cleavage in the neurons is thought to be the endosomes/endocytic organelles [21]. The ϒ-secretase, reported to function at both the plasma membrane and the endosomes, is a complex of four proteins—presenilin (PSEN), presenilin enhancer 2 (PEN2), nicastrin and anterior pharynx defective 1 (APH1). The ϒ-secretase cleaves the Aβ domain of APP in a sequential manner, generating varying lengths of Aβ peptide (from Aβ38 to Aβ42). Along with APP, presenilin 1 and presenilin 2 (PSEN1 and PSEN2), the catalytic subunits of the ϒ-secretase, are the other major class of proteins implicated in familial AD [19]. The mutations of APP are shown to increase its propensity toward the amyloidogeinc pathway, whereas the mutations in PSEN are shown to increase the generation of Aβ42, the more hydrophobic and toxic form of Aβ [20,22,23].

The microRNA-mediated regulation of APP and the proteins influencing its proteolytic cleavage are well studied. In this section, we review the role of microRNAs regulating APP and the secretases, which cleave APP (Fig. 1).

APP

The APP mRNA levels have been shown to be regulated by many microRNAs/microRNA families. MiR-20a family (which includes miR-20a, miR-17-5p and miR-106b), miR-101, miR153 and miR-193b are reported to directly target APP mRNA in cultured neurons and neuronal cell lines [24–27]. The decreased levels of miR-106b and miR153 were also validated in the post-mortem brain samples of AD patients [24,27]. SAMP8 mouse model for age associated AD has also been shown to have increased APP levels, which is correlated with the reduced levels of its target miR-16 [28]. Although many of these studies report the microRNAs targeting APP and their levels being affected in AD, the functional and pathological link between them is not well established.

Along with APP expression, the alternative splicing of APP is also shown to be regulated by microRNAs. Neuronal APP is generally devoid of exon 7 and 8. However, the APP from many AD patients was shown to be inclusive of these exons which is supposed to increase Aβ production. Smith *et al*. showed that this alternative splicing of APP was modulated indirectly by miR124. MiR124 is shown to target the mRNA of polypyrimidine tract binding protein (PTPB1), a global repressor of pre-mRNA splicing leading to increased inclusion of target exons [29,30]. The decreased levels of miR124, as observed in brains of AD patients, were shown to cause an increase in the levels of PTPB1 protein. The increase in PTPB1 protein (repressor of splicing) was correlated with the alternative APP isoform (generated due to lack of splicing of exon 7 and 8) in AD [31]. Although the study is correlative and does not establish the exact link between PTPB1 and APP splicing, it gives interesting insights into alternate ways by which microRNAs can influence the processing of APP mRNA and hence contribute to increased Aβ production. This approach also opens the field to the possibilities by which microRNA-mediated regulation of mRNA splicing can influence disease pathology, other than just affecting the protein levels.

ADAM10

Many studies have reported that the microRNAs targeting alpha-secretase ADAM10 mRNA are upregulated in AD leading to decreased levels of ADAM10 and increased amyloidogenic cleavage. MiR-221, miR-144, miR-451 and miR-140-5p were reported to target ADAM10 mRNA and decrease its expression in neuronal cell lines [32–34]. The increase in miR-144 levels in AD is shown to be due its transcriptional upregulation caused by Aβ. Aβ exposure was shown to activate the transcription factor AP-1, which has putative binding sites 1 kb upstream from the miR-144 transcription start site [32]. Thus, increased production of Aβ upregulates miR-144 through transcriptional activation, decreases ADAM10 levels and prevents non-amyloidogenic pathway. However, the mechanism of how Aβ regulates AP-1 activity is still unexplored. MiR-140-5p was also shown to be upregulated in human AD post-mortem brain samples corresponding to the decreased ADAM10 levels [34].

BACE1

The role of microRNAs in regulating the expression of BACE1 is well documented. MiR-29 family is reported to target BACE1 mRNA by many studies [35,36]. MiR-29a/b-1 cluster was shown to be downregulated corresponding to the increased BACE1 levels in post-mortem brain samples of sporadic AD patients [35]. MiR-29c was also shown to target BACE1 in neuronal cell lines [36]. Another well-studied microRNA targeting BACE1 mRNA is miR-107. Decreased levels of miR-107 were not only observed in the post-mortem brain samples of AD patients but also observed in brain samples of individuals with mild cognitive impairment (MCI)/early AD pathology [37]. The study also conducted *in situ* hybridizations to show that miR-107 decrease was observed in the cerebral cortical lamina (deep cortical layers 5 and 6) coinciding with the plaques and tangles [37]. Other microRNAs that are reported to regulate BACE1 mRNA are miR-124, miR-298, miR-328, miR-485-5p, miR-195 and miR-135a-5p [38–41]. Several of these studies only report the altered microRNA levels in AD, and some of them have tried to link the altered microRNA levels with Aβ accumulation or localization [36]. While many studies successfully show that microRNA levels are dysregulated, there are hardly any studies that show this as the cause. Even in this case, the question of what triggers the microRNA levels to change would always arise. Hence, along with identifying target microRNAs of the crucial proteins, more insights into what triggers the microRNA dysregulation would be important in the future.

Surprisingly, there are very few reports about the role of microRNAs in regulating the expression or activity of ϒ-secretase. Since ϒ-secretase/presenilins have such a crucial causative role in AD, it would be interesting and important to explore the role of microRNA-mediated regulation of PSEN activity.

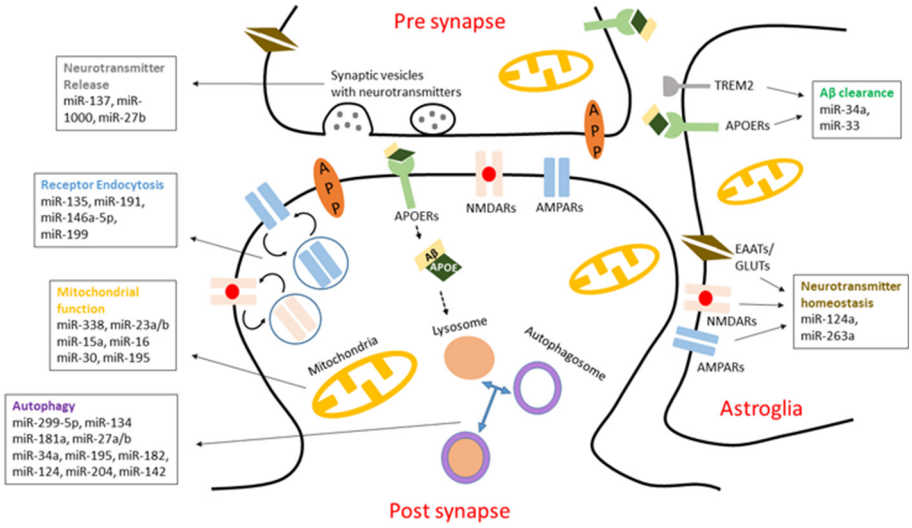

Fig. 2. MicroRNA-mediated regulation of cellular processes affected in dementia pathology. Synapse is the first region at which the defect begins in dementia. Several cellular processes that are required to maintain the proper functioning and integrity of the synapse are affected in dementia. Neurotransmitter homeostasis is a crucial process important for preventing the excitotoxicity observed in dementia. This figure shows the role of microRNAs in regulating this process at the pre-synapse (neurotransmitter release), post-synapse (receptor endocytosis) and in the astroglia (neurotransmitter uptake/clearance). Similarly, microRNAs modulating the process of mitochondrial function and autophagy are also depicted in the figure.

MicroRNAs regulating the proteins associated with AD

Apolipoprotein E

Apart from the primary proteins whose mutations cause the disease, there are other associated proteins that influence the disease progression or pathology by acting either as protective factors or as risk factors. Especially in a disorder like dementia where the sporadic cases are a majority, understanding the regulation upstream of/downstream by such factors is essential. AD has been associated with several such proteins, the most well-studied one being apolipoprotein E4 (APOE4). The E4 isoform of APOE protein is the most well-established risk factor for sporadic AD [42]. APOE is a lipoprotein that is mainly secreted by astrocytes in adult brain and is known to transport cholesterol to neurons by binding to receptors such as LDL-receptor related protein (LRP), apolipoprotein E receptor 2 (Apoer2), low-density lipoprotein receptor (LDLR) and very low-density lipoprotein receptor (VLDLR) [43]. Association of APOE with AD was established when it was shown to bind to Aβ and facilitate its clearance/uptake through the APOE receptors. The two major factors influencing the Aβ binding by APOE are the APOE isoform and the lipidation status of APOE [42]. The risk factor APOE4 is shown to have minimal binding to Aβ, hence having the lowest efficiency of Aβ clearance [44]. Similarly, the binding of APOE to Aβ is shown to be minimal when APOE is not lipidated [44].

One of the studies that has looked at the microRNA-mediated regulation of APOE lipidation indicates the role of miR-33 in this process. The study shows that miR-33 targets ABCA1 (ATP-binding cassette transporter A1), a protein that transfers cellular cholesterol onto APOE for further transport. The increase in miR-33 decreases ABCA1 levels and inhibits its function, hence causing decreased APOE lipidation and impaired Aβ clearance [45] (Fig. 2). Thus, the study suggests an interesting alternate therapeutic approach of using anti-miR-33 to promote Aβ clearance.

Sirtulin 1

Recent studies have emphasized on the role of sirtulin 1 (SIRT1) as a neuroprotective factor against age-related neurodegenerative disorders. SIRT1 is an NAD-dependent deacetylase that also plays a crucial role in regulating transcription depending on the energy availability. SIRT1 has been studied in the context of neurodegeneration after it was observed that the Aβ plaques/amyloid pathology was reduced in the brains of calorie-restricted mice due to the activation of SIRT1 [46]. Follow-up studies have shown that SIRT1 increases the transcription of ADAM10 and also prevents Tau accumulation by deacetylating Tau [47](Fig. 1).

There are reports of decreased SIRT1 levels in AD, which is caused by the increased levels of its target microRNAs like miR-132/212 family [48]. The

study by Gao *et al*. [49] has explained how SIRT1 and miR-134 regulate memory and plasticity, thus showing the implications of downregulated SIRT1 in AD. Their study shows that SIRT1, along with the transcription factor YY1, represses miR-134 by directly binding to the regulatory regions. Downregulation of SIRT1 causes an activation of miR-134, which leads to the translation inhibition of its targets CREB and BDNF, thus impairing memory and plasticity. Along with SIRT1 being regulated by its set of target microRNAs, it also regulates the transcription of few other microRNAs, thus contributing to synaptic plasticity. Such studies give sneak peek into how complex the impact of microRNAs can be on the pathology of dementia.

Triggering receptor on myeloid 2

In last 3 to 5 years, many studies have associated triggering receptor on myeloid 2 (TREM2) function to AD. TREM2 was identified as a receptor for Aβ on glial cells, important for the uptake and clearance of Aβ (Fig. 2) [50]. Most of the Aβ-mediated changes in microglia such as depolarization, inward potassium currents, cytokine secretion and migration were shown to be dependent on TREM2 [50].

The role of miR-34a in regulating TREM2 function is well studied [51,52]. Many NFKB-sensitive proinflammatory microRNAs are shown to be upregulated in AD due to increased activity of NFKB. Microglia-enriched miR-34a is one among them that has binding sites of NFKB in the promoter region and is transcriptionally upregulated in the post-mortem brain samples of AD patients and murine microglial cells [51]. Increase in miR-34a levels is shown to decrease TREM2 levels and impair Aβ clearance [51,52].

MicroRNAs regulating the proteins implicated in FTD

FTD is a broad term that is used to describe a group of disorders involving progressive degeneration of the frontal and temporal lobes of the brain. Unlike AD, the pathological changes in FTD are more heterogeneous containing different kinds of inclusion bodies. Two major kinds of inclusion bodies implicated are –TDP43-ubiquitin–positive inclusion bodies and Tau-positive inclusion bodies [3]. Familial cases of FTD account for one-third of all the FTD cases and the main proteins implicated in familial FTD are TD43, progranulin, Tau and chromosome 9 open reading frame 72 (C9orf72) expansion mutations [3].

TDP43

TAR DNA-binding protein 43 (TDP43) is an RNA/DNA binding protein involved in regulating various steps of RNA metabolism. TDP43 was identified to form complexes with Drosha and Dicer, hence indicating its role in microRNA biogenesis and processing [53]. TDP43 was also shown to have a role in regulating mRNA splicing by binding to the long intronic regions of 239 mouse brain pre-mRNAs. The levels of these transcripts were decreased in the absence of/with mutations in TDP43 indicating RNA degradation due to premature stop codon or unproductive splicing [54]. Through regulating splicing, TDP43 could influence the binding of the microRNAs to their respective mRNA targets as well.

The localization of TDP43 is another aspect that plays a key role in regulating its function. TDP43 is localized majorly in the nucleus with a scant presence in the cytoplasm. Under stress, TDP43 relocates from the nucleus to the cytoplasm forming ubiquitin-positive aggregates. Along the same lines, the study by Zhang *et al*. [55] showed that the iPSC-derived neurons from FTD patients with TDP43 mutations were more sensitive to oxidative stress than control neurons. The patient neurons showed a decrease in the TDP43 levels on oxidative stress and increased localization of TDP43 to the cytoplasm compared to the controls. These neurons also showed a downregulation of pri-miR-9 and miR-9, a brain-enriched microRNA shown to regulate synaptic plasticity [56]. Although the study did not clearly explain the link between TDP43 and these microRNAs, it does indicate that TDP43 mutations can affect the processing of certain microRNAs that contribute to the disease phenotypes.

MicroRNAs that directly regulate TDP43 expression and function are not well studied as most of the studies have emphasized on the role of TDP43 in regulating a repertoire of microRNAs and their processing. The presence of TDP43 inclusion bodies in FTD also supports the important role of TDP43 in RNA metabolism. However, the mechanisms of TDP43 inclusion bodies leading to neurodegeneration are still unclear. The targets of TDP43 and their specificity in contributing to TDP43 mediated neurodegeneration and dementia are yet to be explored as well.

PGRN

Progranulin (PGRN) is another protein recently implicated in familial FTD with TDP43 and ubiquitin aggregates. PGRN is mainly expressed by mature neurons and shown to be important for neuroinflammatory responses and activation of microglia in conditions of stress and injury [57]. One of the recent studies has shown the importance of PGRN in mediating autophagy and hence hypothesized that loss of PGRN hampers the autophagy mediated clearance of TDP43 aggregates [58,59]. Over 30 mutations have been identified in PGRN, all of them

leading to null alleles and loss of functional PGRN [57]. Since this is a relatively new finding, the mechanisms of PGRN mediated FTD and neurodegeneration are not well understood.

There are only few studies that have looked at the role of microRNA-mediated regulation of PGRN. Kocerha *et al*. [60] conducted microarray from frontal cortex of 40 post-mortem brain samples of patients with PGRN mutation FTD. They identified the expression of 20 microRNAs that were dysregulated.

MicroRNAs regulating Tau

Microtubule-associated protein Tau (MAPT) is known to associate with microtubules and promote tubulin assembly. Tau undergoes many modifications such as acetylation, glycosylation, ubiquitination, glycation, polyamination and nitration, but the phosphorylation of Tau is primarily implicated in taupathies [61]. Taupathies are a class of diseases that are caused by hyper-phosphorylation and pathological aggregation of Tau. Most of the taupathies occurring in neocortex are associated with dementia. While mutations in MAPT are one of the major causes implicated in familial cases of FTD with tau aggregates, taupathies are also associated with AD and dementia pugilistica. The hyper-phosphorylated form of Tau is shown to have negative effect on microtubule assembly as it aggregates into paired helical filaments and forms the neurofibrillary tangles [62]. Some of the studies also report a gain of toxic function by hyper-phosphorylated Tau caused by sequestration of other MAPs (MAP1 and MAP2), which leads to microtubule disassembly [61,63,64]. The major kinases of Tau reported are GSK3β, Cdk5 and PKA. The only reported phosphatase of Tau is PP2A [61,62].

The importance of microRNAs in regulating Tau function is well established. The microRNAs which target Tau mRNA and regulate its expression are known such as miR-132/212 family and miR-219 [65,66]. Some of these studies delve on the mechanism of how the microRNAs influence the activity or the levels of the kinases of Tau, hence affecting its phosphorylation (Fig. 1). An interesting study by Absalon *et al*. [67] followed up on two independent observations in AD—(1) miR-26b was upregulated in human AD and MCI post-mortem brains and (2) aberrant cell cycle entry/presence of cyclins and CDKs in post-mitotic neurons. They have proposed a model to connect the two and explain how miR-26b upregulation leads to Tau hyper-phosphorylation and neuron loss. They show that miR-26b targets retinoblastoma (Rb1) mRNA leading to decreased Rb1 protein and increased transcription of S-phase genes. This leads to cell cycle re-entry and translocation of Cdk5 from the nucleus to the cytoplasm. Cytoplasmic Cdk5, a known kinase of Tau, leads to its hyper-phosphorylation. Thus, the study establishes how the upregulation of miR-26b in AD causes cell cycle re-entry in post-mitotic neurons and tau hyper-phosphorylation finally leading to apoptosis [67]. The other kinase of Tau, glycogen synthase kinase 3β (GSK3β) is shown to be regulated by miR-138. MiR-138 directly targets retinoic acid receptor alpha (RARA), which causes a decrease in retinoic acid signaling [68]. As shown by an earlier study [69], decreased retinoic acid signaling leads to increased activity of GSK3β leading to tau hyper-phosphorylation and paired helical filament formation.

Taupathies are also associated with dysregulation of microRNAs. MicroRNAs that are upregulated in pre-symptomatic taupathy models are reported [70]. It is also shown that the overexpression of mutant Tau is sufficient to cause the dysregulation of many miRNAs with miR-142 being one of them. Although the exact mechanism of miRNA dysregulation is not well understood, overexpression of mutant Tau is shown to cause neuroinflammation and reactive astrocytes [70]. One of the top miRNA that was upregulated on overexpression of mutant Tau was miR-142. The overexpression of miR-142 caused altered Stat3 signaling, neuroinflammation and gliosis, similar to the overexpression of mutant Tau [70]. This is one of the studies that shows how the mutations in Tau can cause the dysregulation of microRNAs, which in-turn alters the signaling pathways and leads to disease progression [70]. Overall, while there are many microRNAs involved in regulation of tau levels and phosphorylation, tau also regulates certain microRNAs, which explains the complex role of microRNA dysregulation in taupathies.

Role of MicroRNAs in Regulating the Cellular Processes Contributing to Dementia

Dementia pathology is quite complex at the cellular level. Many cellular and molecular processes are affected including mitochondrial function, energy production, reactive oxygen species (ROS) management, autophagy and neurotransmitter homoeostasis. Dysregulation of these cellular processes is a common downstream effect in both familial and sporadic cases of dementia. Hence, understanding how these processes are regulated and maintained also becomes very crucial. The role of microRNAs in regulating many steps of these processes is well studied. In the following section, we aim to review microRNA-mediated regulation of cellular processes that are defective in dementia (Fig. 2), emphasizing and extending on the role of microRNAs in the regulation of proteins directly or indirectly implicated in these cellular and molecular processes.

Mitochondrial function—oxidative stress and energy production

Mitochondrial dysfunction is one of the major cellular pathway/component affected in dementia, especially in case of AD. Several changes are observed in AD with respect to mitochondrial morphology, fission–fusion dynamics, metabolism and functioning [71]. A decline in mitochondrial function, accumulation of mtDNA mutations and increased ROS are considered to be the major causative reasons and triggering factors for sporadic AD [72]. Aβ is shown to localize to the mitochondria and cause decreased mitochondrial membrane potential and activation of apoptotic pathways [6]. Studies have also reported increased complex III and decreased complex IV activity of mitochondria in the brains of transgenic mice model, leading to increased production of ROS and decreased synthesis of ATP [6]. The increased production of ROS is considered to be a major contributing factor for the oxidative stress observed in AD causing oxidation of cellular RNA, proteins and lipids leading to their abnormal functioning or degradation [5,73,74]. Along with increased oxidative burden, the decreased cellular energy is also considered to be a major factor contributing to the impaired functioning and disability of the cell to cope with stress.

The role of microRNAs in regulating some of these mitochondrial functions is studied. For example, cytochrome *C* oxidase IV (COXIV), a nuclear-encoded electron transport chain protein is shown to be regulated by miR-338 in neuronal cells [75]. Similarly, miR-23a/b are shown to target glutaminase, an enzyme that converts glutamine to the TCA cycle substrate glutamate, hence regulating mitochondrial metabolism [76]. miR-15a and miR-16-1 are shown to have a role in regulating mitochondria mediated apoptosis (cytochrome *C* release) by targeting Bcl2 [77]. miR-30 family is reported to regulate mitochondrial fission by targeting p53 and Drp1 [78]. In SAMP8 mouse model for aging, mfn2 (mitofusin 2) mRNA levels were shown to be downregulated in the hippocampus leading to decreased mitochondrial membrane potential and activity [79]. This was shown to be dependent on increased levels of miR-195, a microRNA previously implicated in AD pathology. These reports suggest how dysregulation of microRNAs can impair mitochondrial function and lead to pathology (Fig. 2).

The prevalent idea is that microRNAs present in the mitochondria are nuclear encoded and imported. Some studies have isolated pure and intact mitochondria to show that mitochondria have a cell type-dependent unique enriched pool of microRNAs (independent of cellular abundance of microRNAs) [80]. Along with the microRNAs, mitochondria also harbor miRISC proteins like argonaute2 (AGO2), hence acting also as a hub of signaling complexes. In polarized cells like neurons, mitochondria are actively transported to the processes to meet the local energy demands. Along with the mitochondria, the associated microRNAs and RISC proteins are also transported, creating an enriched environment for local translation regulation [80].

Autophagy and mitophagy—clearance pathways

Autophagy

Most types of dementia are associated with progressive accumulation and aggregation of misfolded proteins and peptides. This accumulation can happen due to the imbalance created either at the step of synthesis or at the stage of clearance. Most of the proteins identified to be responsible for familial cases of dementia mainly alter the synthesis and/or aggregation of the misfolded proteins and peptides [81]. In the past few years, several groups have also looked at how the clearance pathways are affected in dementia, a defect that seems to be a common downstream phenotype among both familial and sporadic cases. Of the clearance mechanism, the dysregulation of autophagy–lysosomal pathway is widely investigated in dementia [81]. Autophagy–lysosomal pathway is a chain of events that is responsible for clearance of misfolded and aggregated proteins and dysfunctional organelles in the cell. Along with its contribution in maintaining the homeostasis in the cell, autophagy is crucial for recovering resources for the cell under conditions of stress such as nutrient starvation, oxidative stress or neuronal excitotoxicity (most of which are observed in cases of dementia). Many studies have shown that autophagy is up-regulated in the post-mortem human brain samples as well as in transgenic mouse models of AD [82]. Presence of abnormal large autophagosomes, as a result of defective lysosome fusion is also reported [83]. Presenilins, the ϒ-secretase subunit implicated in AD pathology, are shown to modulate autophagy as well [84–89]. The loss of presenilin activity causes impairments in lysosomal acidification and biogenesis finally leading to increased autophagosomes and impaired autolysosomes [84,85]. Although the link between presenilins and autophagy is well established, the other upstream regulators of autophagy-mediated defects in AD are not well understood.

Each step in the process of autophagy is regulated by several microRNAs—autophagy induction regulated by miR-885-3p; vesicle nucleation regulated by miR-182, miR-34a, miR-195, miR-21 and miR-205; autophagosome membrane elongation regulated by miR-375 and miR-204; and autophagosome maturation targeted by miR-98, miR-124, miR-204 and miR-142 [90]. Many of these microRNAs such as miR-124, miR-34a and miR-195 are reported to be dysregulated in AD, indicating that they could be

potentially influencing some steps of autophagy (Fig. 2). Very few studies give mechanistic insight into how microRNA-mediated dysregulation of autophagy can lead to AD pathology [91]. One such study showed that miR-299-5p levels in the AD mouse brain are low and intracerebral injections of miR-299-5p act as a neuroprotective agent and help them improve their performance in cognitive tests. They explained that miR-299-5p targets ATG5, the protein important for autophagosome closure, and inhibits it; thereby attenuating the enhanced autophagy and ATG5-mediated apoptosis. Similarly, the use of antago-miR-134 restored abnormal autophagy in epileptic mouse models by reducing oxidative stress and improving mitochondrial function. Oxidative stress being the reason for abnormal autophagy in this system, antago-miR-134 treatment restored it by decreasing the levels of autophagy associated proteins such as ATG5 and Beclin1 [92]. Although this study was conducted in the model of epilepsy, the defects of oxidative stress, mitochondrial dysfunction and abnormal autophagy are common and can be extrapolated to dementia as well.

While there are microRNAs that target and regulate different steps of autophagy, autophagy itself also acts as a mechanism to regulate the microRNA loading. The precursor miRNAs are double-stranded RNA duplex which are a loaded onto a complex of Dicer and AGO2 (RISC components) for processing into a single-stranded mature miRNA. The Dicer–AGO2 complexes, which are not loaded with the microRNAs, are degraded by autophagy, thereby autophagy acts as a checkpoint of microRNA loading and removal of inactive complexes [93]. Hence, the defective autophagy in dementia could also affect the process of microRNA homeostasis, leading to more a global dysregulation. While some groups report that promotion of autophagic flux could be beneficial by removal of defective components of the cell, other groups contradict this by indicating that it is more helpful to inhibit autophagy, which is already defective. Once we know more about the microRNAs which regulate autophagy in dementia, the role of autophagic flux (its upregulation/downregulation) can be understood better.

Mitophagy

The damaged and dysfunctional mitochondria are cleared through the mechanism of mitophagy (autophagy of the mitochondria), ensuring proper mitochondrial functioning within the cells. In case of dementia, studies have shown that the process of mitophagy is affected. This impaired clearance of dysfunctional mitochondria is hypothesized to be one of the ways by which increased ROS, decreased ATP production and metabolism are aggravated in AD. The mechanism of mitophagy is quite well understood. PINK1 (Pten-induced putative kinase 1), which is maintained low at physiological levels, gets upregulated and stabilized on mitochondrial damage. PINK1 activates Parkin and leads to translocation of Parkin from the cytosol onto the damaged mitochondria. Parkin, an E3 ubiquitin ligase, tags the damaged mitochondria for autophagy through ubiquitination of several of its proteins [94].

The crucial proteins involved in mitophagy such as PINK1 and Parkin are known to be regulated by specific microRNAs. MiR-181a was shown to target Parkin1 and act as an inhibitor of mitophagy under normal conditions. The use of uncouplers was shown to downregulate miR-181a allowing the expression and translocation of Parkin1 [95]. Similarly, miR-27a/b targets PINK1 and regulates mitophagy under normal conditions by keeping PINK1 levels low. Under acute mitophagy, miR-27a/b levels drop causing increase in PINK1 levels. Interestingly, when the cells are subjected to chronic mitophagic flux, the levels of miR-27a/b increase significantly and activate a negative feedback loop to prevent excessive depletion of mitochondria [96]. Hence, mitophagy is not just a process of removing the damaged mitochondria, but it also involves maintaining homeostasis of mitochondrial functioning in the cells, suggesting how the dysregulation of microRNAs in dementia could lead to a drastic imbalance with regard to the cellular metabolism.

Glutamate homeostasis and excitotoxicity

Glutamate-mediated excitotoxicity is another phenotype implicated in dementia cases, especially in AD. Glutamate being the major excitatory neurotransmitter in the central nervous system, has two different kinds of receptors—ionotrophic (iGluRs comprising of NMDARs, AMPARs and kianate receptors) and metabotrophic (mGluRs). The synaptic transmission mediated by glutamate involves the following steps—fusion of vesicles containing glutamate with the pre-synaptic membrane, release of glutamate from the pre-synapse, depolarization of the post-synaptic terminal upon glutamate binding, calcium influx and activation of signaling cascades [97]. Many pre-synaptic and post-synaptic processes linked to glutamate signaling are shown to be affected in AD, which finally leads to synaptic dysfunction and neurotoxicity. At the pre-synapse, Aβ is reported to increase the potassium-evoked glutamate release and hence the network activity in the hippocampal slices [98]. Aβ interferes with the calpain–CDK5 pathway leading to defective endocytosis of synaptic vesicles [99,100]. This is proposed to be the mechanism by which Aβ alters the ratio of recycling pool and resting pool of synaptic vesicles and affects the release probability [99,100]. The role of Aβ in causing post-synaptic defect is relatively well studied. There are many detailed

studies in the field of AD explaining how Aβ mediated spine loss is dependent on excessive activation of synaptic and extra-synaptic NMDARs [101,102]. Aβ oligomers are shown to directly bind to NMDARs causing excessive calcium influx leading to mitochondrial calcium overload and apoptosis [103]. Conversely, Aβ from cell-secreted source is shown to decrease the calcium influx through NMDAR, hence inducing long-term depression and spine shrinkage/retraction [104]. Overall, the excitotoxicity caused by glutamate is mainly attributed to the overstimulation of the receptors leading to increased influx of calcium and sodium, finally causing cell death [105].

MicroRNA-mediated regulation of neurotransmitter homeostasis can be broadly classified into two major groups.

MicroRNAs regulating the expression and endocytosis of the receptors

MicroRNAs directly regulate expression of the glutamate receptors at the post-synapse which influences plasticity and excitotoxicity. The expression of AMPAR subunit GluA1 is shown to be regulated by miR-501-3p and miR-92a [106,107]. Similarly, AMPAR subunit GluA2 expression is reported to be regulated by miR-223, miR-124 and miR-181 [108–110]. There are over 20 microRNAs reported to regulate the expression of NMDAR subunits NR2A and NR2B, which would directly influence the calcium influx through the receptor [111]. Along with maintaining the receptor levels at basal condition, many microRNAs regulate the expression of receptor subunits in an activity-dependent manner as well. This plays an important role in modulating synaptic strength and plasticity. For example, the dendritic increase in miR-501-3p on NMDAR stimulation is important for decrease in GluA1 translation and long-term spine remodeling. Similarly, miR-137, which also targets and inhibits GluA1 expression, was shown to be upregulated on mGluR5 stimulation, helping in mGluR mediated LTD in hippocampal synapses. The other slightly indirect but very interesting way by which microRNAs influence excitotoxicity is by regulating the receptor expression in glial cells (Fig. 2). The astroglial also express glutamate receptors, at varying compositions and levels as that of neurons, helping in glutamate homeostasis at the synapse. MiR-263a was shown to be critical for maintaining low levels of Nmdar1, Nmdar2 and Grik in the glial cells of *Drosophila*. Any mutations in miR-263a lead to the overexpression of these receptors on the glia, increasing the sensitivity of glia for glutamate causing excitotoxicity, dysfunction and death [112]. This would cause an imbalance of glutamate and eventually affect the neuronal function as well.

Another aspect that regulates synaptic plasticity and excitotoxicity is the endocytosis of the receptors (mainly AMPARs) at the post-synapse. Several microRNAs are reported to target the proteins directly involved in the process of endocytosis such as Rab5 and clathrins [113,114], in turn influencing AMPAR endocytosis (Fig. 2). Along with these, post-synaptic proteins like MAP1B and Arc are also known to influence AMPAR trafficking and internalization on synaptic activity by interacting with endocytic machinery or cytoskeletal elements [115,116]. For example, miR-146a-5p targeting MAP1B was shown to be downregulated in hippocampal neurons on mGluR stimulation. This increases MAP1B levels on mGluR stimulation, activates Rac1 in the synaptic compartments and enables actin remodeling [117]. All these processes are critical for AMPAR endocytosis required for maintaining mGluR-LTD [118]. The dysregulation of any of these microRNAs may lead to defective endocytosis of AMPARs, especially on synaptic activity, which may contribute to impaired synaptic plasticity and excitotoxicity [97].

MicroRNAs regulating the neurotransmitter release and clearance

At the pre-synaptic side, regulation of vesicle formation and trafficking plays a critical role in preventing excitotoxicity and neurotransmitter balance [119]. The role of microRNAs in regulating this aspect is not as well explored as its role at the post-synaptic side. An extensive study showed the role of *Drosophila* miR-1000 or mouse miR-137 in controlling the pre-synaptic glutamate release by targeting vesicular glutamate transported (VGlut) expression [120]. Any mutations or misregulation of miR-1000 were shown to lead to excess glutamate release causing excitotoxicity. Similarly, miR-27b was shown to target Synaptotagmin-1, a calcium sensor protein in the synaptic vesicles, which triggers evoked and spontaneous neurotransmitter release [121]. Although many proteins that are involved in vesicle trafficking and glutamate release (such as Synaptotagmin1, Syanapsin1, Syntaxin1A) are affected in dementia [122], there are no studies showing how microRNA-mediated dysregulation can influence this.

Astroglial cells are involved in clearance of glutamate from the synaptic cleft, hence ensuring recycling of the neurotransmitter and prevention of neurotoxicity. Exosomes are extracellular vesicles released by the cells, known to contain proteins, lipids and RNA species. They are often used as medium of communication between the cells (including neurons and glia). The exosomes secreted by primary neurons are shown to contain miR-124a, which is readily taken up by primary astrocytes. This acts indirectly (through other astroglial factors) to increase the expression of EAAT2 (excitatory amino acid transporter 2) on the astrocytes, hence enabling

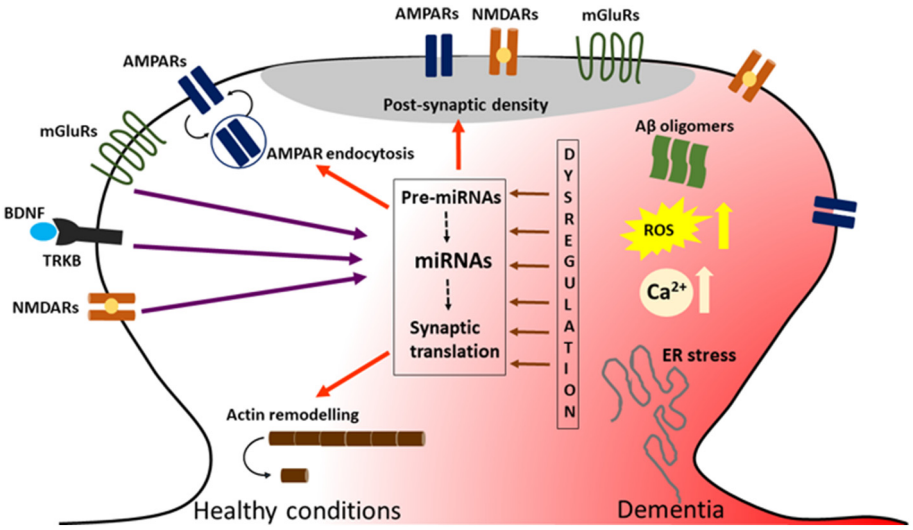

Fig. 3. The role of microRNAs in synaptic signaling and their potential implication in dementia. MicroRNAs are localized to synapses and can also be generated from their precursors locally. Here they regulate the expression of several synaptic proteins and control many important processes such as AMPA receptor endocytosis and their surface expression, actin cytoskeletal dynamics and organization of postsynaptic density (PSD). MicroRNA-mediated regulation at synapse is controlled by signaling through glutamate (NMDAR and mGluR) and trophic factor factors (such as BDNF). Factors implicated in dementia such as increased ROS, defective calcium homeostasis and ER and mitochondrial stress can have adverse effect on the microRNA-mediated regulation. Defective microRNA regulation will have a significant impact on synaptic function and contribute to the cognitive loss in dementia.

better clearance of glutamate from the synaptic cleft [123]. Similarly, microRNAs in astrocyte derived exosomes are also shown to affect neuronal functions [124]. Along with the set of microRNAs that would directly regulate the expression of transporters on the glia, the mechanism of exosomes that allows the neuronal miRNAome to influence the receptors/transporters on the glial cells is very intriguing. This also gives a new perspective of how the imbalance of microRNAs in non cell autonomous manner. This understanding would be all the more interesting and important in a system like neurons, which have highly connected tripartite synaptic networks. Hence, apart from regulating proteins that are directly involved in dementia pathology, microRNAs also play a crucial role in regulating other molecular processes affected in dementia.

Dementia and Synaptic Translation

Synaptic defects are well documented in both AD and FTD and are discussed extensively in recent reviews [11,125,126]. Synaptic dysfunction is the primer of dementia where progressive neurodegeneration is a common ultimate marker. Understanding the neurodegeneration and cytotoxic factors contributing toward that effect has garnered major attention of the field, while research on synaptic dysfunction is gaining traction only recently. In familial cases (which currently forms only small minority) where mutations lead to defective protein function and sporadic cases where origin of the disease is unclear, synapse is the primary site for the manifestation of cognitive loss and dementia. Mitochondrial defects, increased oxidative stress and abnormal/excessive protein aggregation are thought to be some of the early events affecting the neuronal activity in these cases. All these factors have disproportionally high impact on synapses compared to the rest of nervous system. However, a gap in our understanding is why exactly should factors have a disproportional impact at synapse which in turn triggers the pathology? A key insight might be obtained by studying the impact of these factors on the regulation of synaptic protein synthesis.

Activity-mediated protein synthesis is an important component of synaptic signaling and plasticity [127–129]. Proteins involved in coupling of chemical and electrical signaling, master regulators that integrate multiple receptor pathways, modulators of cytoskeletal rearrangement and endo/exocytosis are among the ones that are synthesized on synaptic activity (Fig. 3). Translation regulation of these proteins is well established to be important for many forms learning and memory consolidation. Multiple factors that are directly linked to AD and FTD pathology such as increased ROS, defective energy balance, increased ER and mitochondrial stress due to protein aggregation can have significant impact on synaptic protein synthesis. However, the studies to explore the link between the activity-

mediated protein synthesis and cognitive loss leading to dementia have only just begun [130,131]. A recent study reported that oxidative stress can affect protein synthesis signaling at the synapses. Ahmad *et al*. [130] showed that activity-mediated translation is deficient not only in the mouse models of AD but also in the synptoneurosomal preparations from the patient brain samples. They went on to show that increased ROS in the mouse model of AD affects synaptic Akt1 signaling, which is responsible for the loss of activity-mediated translation. Another interesting study [131] found that phosphorylation of the translation initiation factor eIF2α in AD patient and mouse models leads to reduced global translation. Increased phosphorylation in this case was attributed to two upstream kinases (PERK and GCN2), which respond to stress signal including increased ER stress (due to misfolded and aggregated proteins) and oxidative stress. Increased eIF2α phosphorylation abrogates activity-mediated translation at the synapse and is thought to be responsible for cognitive defects in Alzheimer's dementia. Inhibition or removal kinases acting in response to stress could restore protein synthesis and synaptic plasticity in the animal model [131]. Apart from this, increased oxidative stress also causes multiple molecular damages at the synapse by oxidation of many proteins and RNA molecules. By their sheer abundance, the ribosomes will be among the most affected, which results in decreased translation efficiency [12,73]. While this may affect the whole cell, synapses will be particularly vulnerable since they are the sites of increased oxidative stress and due to their acute translation demands [126]. However, all these studies focus on general translation defect at the synapse and do not dwell into the translation of specific synaptic proteins or translation downstream of specific receptors where the direct role of microRNAs can be established.

MicroRNAs play a significant role in spatio-temporal regulation of mRNA translation in response to synaptic activity [132,133]. Like mRNAs, several microRNAs are shown to be actively transported and localized to distal dendrites and even enriched in the synaptic compartments. Here they may reversibly inhibit translation of synaptic mRNAs and link their expression with specific synaptic signaling through trophic factors or neurotransmitters (Fig. 3). MiR-134 and miR-138 were shown to regulate Limk1 and APT1 in response to external cues and control the architecture of spines [134–136]. MiR-132, miR-125a and miR-125b are reported to regulate the translation of many important synaptic proteins such as PSD-95 and subunits of NMDA receptors [18,137].

There is a long list of microRNAs that are thought to have a significant influence on synaptic functions [132]; among them few are particularly interesting from the perspective of dementia. The potential role of miR-124 in dementia is particularly interesting. MiR-124 is highly expressed in neurons and seems to influence many aspects of neuronal differentiation, development and plasticity [138,139]. Gascon *et al*. [140] reported a decrease in miR-124 in frontal cortex of FTD patients and in iPSC-derived neurons from patients. They showed that miR-124 targets AMPA receptor subunit mRNA, and this leads to an increased expression of GluA2 containing calcium impermeable AMPA receptors. The reduced calcium signaling was partially responsible for behavioral deficits in the mouse model of FTD. Many intriguing issues remain unsolved here like the link between the mutations causing FTD to decreased expression of miR-124, possible mutation in miR-124 gene as a cause of FTD and differential effect of miR-124 on GluA subunit expression and calcium signaling in specific regions of the brain [141]. However, what makes miR-124 particularly interesting is its role in regulating the expression of GluA (AMPA) receptor subunits and hence its composition and calcium permeability at the synapse. AMPA receptors are the primary contributors of the electrical activity at the postsynaptic compartment and a key component of many forms of synaptic plasticity. Other glutamate receptors such as mGluR and NMDAR exert their effect on synaptic plasticity by manipulating the translation and surface expression of AMPA receptors (Fig. 3). Thus, miR-124-mediated regulation of GluA subunits is likely to have a much broader implication on synaptic defects in both FTD and AD. Potential alteration in miR-124, GluA subunit expression and GluA mediated calcium signaling in familial and sporadic AD and FTD cases would be an interesting area to explore further.

Apart from mature microRNA, their precursors are also reported to be localized to the dendrites and synaptic terminals [142,143]. This facilitates the dynamic changes in the availability of microRNAs in the synaptic compartments based on the neuronal activity [143]. Hence, microRNAs regulate synaptic translation at multiple levels and are integrated with synaptic activity. Currently, we have very little understanding about the correlation of synaptic defects in dementia with microRNAs involved in synaptic translation. A comprehensive study about the changes in the microRNAs involved in synaptic translation in animal models and patient samples of dementia would be highly rewarding, not only in understanding the molecular pathology but also to potentially use them as biomarkers for the early detection in sporadic cases.

MicroRNAs as Biomarkers

The identification of early, reliable, specific and non-invasive biomarkers has always been a

Table 1. MicroRNA biomarkers of dementia pathology

MicroRNAs	Up/down regulated	Source	Pathology	Reference	Additional correlates/therapeutic approach
miR-127-3p	Up	Serum	AD	[144]	
	Down	CSF	AD		
	Up	Plasma	FTD		
miR-184	Up	Serum	AD	[140]	
	Down	CSF	AD		
miR-708-3p, miR-9-3p	Down	CSF	AD	[140]	Decrease in microRNA levels was correlated with increase in Braak stages
miR-16-5p, miR-183b-5p	Down	Serum	AD	[140]	Decrease in microRNA levels was correlated with increase in Braak stages
miR-9-3p, miR-181a/b-5p, miR-181d	Down	CSF	AD	[140]	Decrease in microRNA levels was correlated with increase in neurofibrillary tangle density
Let-7i-3p	Up	Serum	AD	[140]	Changes in microRNA levels correlated with increase in neurofibrillary tangle density
miR-10a-5p	Down				
miR-195-5p	Down	CSF	AD	[140]	Changes in microRNA levels correlated with increasing plaque density
miR-30c-5p	Up				
miR-30b-5p, miR-106a-5p	Down	Serum	AD	[140]	Decreasing microRNA levels correlated with increasing plaque density
miR-29b	Down	Serum	AD	[145]	Decrease correlated with increased transcription factor Sp1 which can lead to further increase in APP and BACE1
miR-206, miR-132	Down	Serum	MCI	[146]	Correlated with decreased SIRT1 and BDNF
miR-93, miR-146a	Up	Serum	MCI, VD	[147]	
	Down	Serum	AD		
miR-31, miR-143	Down	Serum	MCI, VD, AD	[147]	
miR-210	Down	Serum, CSF	MCI, AD	[148]	
miR-132 family (miR-132, miR-128, miR-874) and miR-134 family (miR-134, miR-323-3p, miR-382)	Up	Plasma	MCI, AD		
miR-204-5p, miR-632	Down	CSF	FTD		

challenge in the field of dementia. Most of the methods used for confirmatory diagnosis for dementia (especially AD) involve autopsies. The current important biomarkers used for AD are decreased Aβ42 and increased phosphor-tau in the CSF [125]. Even this involves invasive lumbar punctures, and also they do not identify the disease before the cognitive decline has begun. Recently, many microRNAs are used as biomarkers for early and easy detection of diseases, owing to their cell specific pathological functions and regulations [125]. Peripheral blood biomarkers are ideal candidates as they are easily accessible, non-invasive and cost-effective. There are many studies published reporting the identification of novel microRNA biomarkers from blood/serum for detection of MCI and AD [144]. MicroRNAs that are used as biomarkers for MCI also provide a big advantage of early detection of AD. The field of microRNA biomarkers is heavily focused toward AD, and there are very few studies reporting biomarkers for FTD and other forms of dementia. Some of the studies that have compared the microRNA biomarker signatures between blood and CSF show that there is no overlap between the two, and they also suggest that the biomarkers from CSF could be more stable than the blood [145].

Many studies have not validated the proposed microRNAs as biomarkers and also lack proper controls. Similarly, how universal are these biomarkers and would they hold true for all populations are another questions that have not been addressed. Considering this, we have critically reviewed and listed few candidate microRNA biomarkers that have been identified using proper controls (Table 1). However, there are many reviews that have focused solely on this topic and provide a more comprehensive collection of all the biomarkers [144,146–148]. The idea we want to convey is how microRNAs can be used as biomarkers and correlated with certain pathological phenotypes.

Conclusions

MicroRNAs are versatile regulatory molecules that influence almost every aspect of cellular function. Due to their omnipresence and huge impact on protein synthesis, the role of microRNAs is studied extensively in many disorders, particularly in cancer. The interest about the role of microRNAs in the disorders of nervous system is only beginning to gain momentum. The microRNA-mediated regulation in dementia involves two important aspects—first, the translation dysregulation of individual proteins that can trigger the disease, and second, dysregulation of many cellular processes where microRNAs are involved which can further

Table 2. MicroRNAs implicated in regulating multiple proteins/processes involved in dementia

microRNAs	Processes or protein regulated by the microRNAs
miR-124	• APP splicing [28] • BACE1 and GluA2 (AMPAR subunit) levels [34,106,135] • Autophagosome maturation [86] • Glutamate clearance (EAAT2 levels in astrocytes) [118]
miR-195	• BACE1 levels [37] • Mitochondrial membrane potential and activity (mitofusin levels) [75] • Autophagy (vesicle nucleation) [86] • Biomarker for increased plaque density [140]
miR-132/212 family	• Tau levels [62] • SIRT1 levels [44] • BDNF levels [146]
miR-134	• SIRT1 and BDNF levels [45] • Oxidative stress and autophagy [88] • Spine morphology [137]
miR-181a	• Mitophagy (Parkin expression) [91] • GluA2 (AMPAR subunit) expression [104] • Biomarker for increased neurofibrillary tangle density [140]
miR-34a	• Aβ clearance (TREM2 levels) [47] • Autophagy (vesicle nucleation step) [86]
miR-29a/b/c	• BACE1 levels [32,33] • APP levels [145]
miR-16	• APP levels [27] • Mitochondria mediated apoptosis (Cyt release) [73]
miR-27a/b	• Mitophagy (PINK1 expression) [92] • Neurotransmitter release (Synaptotagmin expression) [116]

aggravate it. It is now established that the expressions of many individual proteins involved in dementia such as APP, β and α secretases, Tau and the kinases which phosphorylate Tau are regulated by microRNAs. In many cases, there is substantial evidence about the altered microRNA levels correlating with the dysregulated expression or function of proteins leading to AD and FTD. However, still there is lack of understanding about the cause for the altered levels of these microRNAs. Reports on how the mutations in the genes expressing the microRNAs/microRNAs clusters can cause the disorder are also lacking. This is an area that needs more concerted efforts. Understanding the role of microRNAs in dysfunction of cellular processes such as autophagy, energy metabolism and neurotransmitter homeostasis is of great importance for dementia research. These processes are common downstream effectors in most cases of dementia irrespective of their origin. Hence, in sporadic cases of AD and FTD (which still forms the overwhelming majority), regulation of these processes through microRNAs can provide important insight into understanding the molecular pathophysiology. Another interesting aspect to consider is that apart from being regulated by microRNAs, many of these processes/proteins that are implicated in dementia also regulate microRNA biogenesis and function. Hence, any dysregulation of these leads to a global change in the microRNAome.

Regulation of synaptic protein synthesis is one of the least explored areas in dementia research, which hold a great potential. Synaptic translation is a very dynamic process where neuronal activity determines the protein synthesis, which in turn regulates the neuronal network. MicroRNAs play a key role in regulating synaptic translation, and any disturbance in this adversely affects the synaptic function. The implication of this process in dementia needs to be studied more rigorously as it may explain the molecular cause of synaptic dysfunction and may turn out to be the primary cause of progressive loss of cognition.

One interesting outcome of reviewing the role of microRNAs in dementia is the repeated appearance of a small number of microRNAs (Table 2) in several independent and unrelated studies. Some of these microRNAs such as miR-124, miR-132 and miR-134 are also widely studied for their role in synaptic structure and function. The repeated appearance of these microRNAs in dementia studies again points to the importance of synaptic translation regulation as a potential cause of the molecular pathology. Also, these microRNAs could be good molecular markers for diagnosis, as already reported in some cases (Table 1). The possibility of microRNAs as a therapeutic tool for dementia is still unclear since they are still not proven to be causative agents. It may also be difficult to manipulate them without collateral damages to their versatile functions. Overall, microRNAs are definitely a very valuable tool to explore the proteins and processes that are dysregulated and provide an important insight into molecular pathology of dementia.

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Abbreviations used:

AD, Alzheimer's disease; FTD, fronto-temporal dementia; ER, endoplasmic reticulum; miRISC, microRNA-induced silencing complex; APP, amyloid precursor protein; APOE, apolipoprotein E; SIRT1, sirtulin 1; TREM2, triggering receptor on myeloid 2; TDP43, TAR DNA-binding protein 43; PGRN, progranulin; MAPT, microtubule-associated protein Tau; ROS, reactive oxygen species; MCI, mild cognitive impairment.

References

[1] J.T. O'Brien, A. Thomas, Vascular dementia, Lancet (London, England) (2015), https://doi.org/10.1016/S0140-6736(15)00463-8.

[2] J. Hardy, A hundred years of Alzheimer's disease research, Neuron 52 (2006) 3–13, https://doi.org/10.1016/j.neuron.2006.09.016.

[3] F.W. Rohlfing, R.K. Tu, Genetics of frontotemporal dementia, Am. J. Neuroradiol. (2017), https://doi.org/10.3174/ajnr.A4972.

[4] D.H.W. Lau, N. Hartopp, N.J. Welsh, S. Mueller, E.B. Glennon, G.M. Mórotz, A. Annibali, P. Gomez-Suaga, R. Stoica, S. Paillusson, C.C.J. Miller, Disruption of ER-mitochondria signalling in fronto-temporal dementia and related amyotrophic lateral sclerosis, Cell Death Dis. (2018), https://doi.org/10.1038/s41419-017-0022-7.

[5] C.S. Atwood, M.E. Obrenovich, T. Liu, H. Chan, G. Perry, M. A. Smith, R.N. Martins, Amyloid-β: a chameleon walking in two worlds: a review of the trophic and toxic properties of amyloid-β, Brain Res. Rev. 43 (2003) 1–16, https://doi.org/10.1016/S0165-0173(03)00174-7.

[6] I.G. Onyango, S.M. Khan, Oxidative stress, mitochondrial dysfunction, and stress signaling in Alzheimer's disease, Curr. Alzheimer Res. 3 (2006) 339–349.

[7] A. Grimm, K. Friedland, A. Eckert, Mitochondrial dysfunction: the missing link between aging and sporadic Alzheimer's disease, Biogerontology 17 (2016) 281–296, https://doi.org/10.1007/s10522-015-9618-4.

[8] L. Guo, J. Tian, H. Du, Mitochondrial dysfunction and synaptic transmission failure in Alzheimer's disease, J. Alzheimers Dis. 57 (2017) 1071–1086, https://doi.org/10.3233/JAD-160702.

[9] K.F.S. Bell, A. Claudio Cuello, Altered synaptic function in Alzheimer's disease, Eur. J. Pharmacol. 545 (2006) 11–21, https://doi.org/10.1016/j.ejphar.2006.06.045.

[10] S.W. Scheff, M.A. Ansari, E.J. Mufson, Oxidative stress and hippocampal synaptic protein levels in elderly cognitively intact individuals with Alzheimer's disease pathology, Neurobiol. Aging 42 (2016) 1–12, https://doi.org/10.1016/j.neurobiolaging.2016.02.030.

[11] G. Sobue, S. Ishigaki, H. Watanabe, Pathogenesis of frontotemporal lobar degeneration: insights from loss of function theory and early involvement of the caudate nucleus, Front. Neurosci. 12 (2018) 1–9, https://doi.org/10.3389/fnins.2018.00473.

[12] K. Hernández-Ortega, P. Garcia-Esparcia, L. Gil, J.J. Lucas, I. Ferrer, Altered machinery of protein synthesis in Alzheimer's: from the nucleolus to the ribosome, Brain Pathol. 26 (2016) 593–605, https://doi.org/10.1111/bpa.12335.

[13] G. Shukla, J. Singh, S. Barik, MicroRNAs: processing, maturation, target recognition and regulatory functions, Mol. Cell. Pharmacol. (2011), https://doi.org/10.1097/OPX.0b013e3182540562.The.

[14] A. Emde, E. Hornstein, miRNAs at the interface of cellular stress and disease, EMBO J. (2014), https://doi.org/10.15252/embj.201488142.

[15] M.R. Fabian, N. Sonenberg, The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC, Nat. Struct. Mol. Biol. (2012), https://doi.org/10.1038/nsmb.2296.

[16] J. Krol, I. Loedige, W. Filipowicz, The widespread regulation of microRNA biogenesis, function and decay, Nat. Rev. Genet. (2010), https://doi.org/10.1038/nrg2843.

[17] P. Kundu, M.R. Fabian, N. Sonenberg, S.N. Bhattacharyya, W. Filipowicz, HuR protein attenuates miRNA-mediated repression by promoting miRISC dissociation from the target RNA, Nucleic Acids Res. (2012), https://doi.org/10.1093/nar/gks148.

[18] R.S. Muddashetty, V.C. Nalavadi, C. Gross, X. Yao, L. Xing, O. Laur, S.T. Warren, G.J. Bassell, Reversible inhibition of PSD-95 mRNA translation by miR-125a, FMRP phosphorylation, and mGluR signaling, Mol. Cell (2011), https://doi.org/10.1016/j.molcel.2011.05.006.

[19] C. Haass, C. Kaether, G. Thinakaran, S. Sisodia, Trafficking and proteolytic processing of APP, Cold Spring Harb. Perspect. Med. 2 (2012) 1–25, https://doi.org/10.1101/cshperspect.a006270.

[20] Y. Zhang, R. Thompson, H. Zhang, H. Xu, APP processing in Alzheimer's disease, Mol. Brain 4 (2011) 3, https://doi.org/10.1186/1756-6606-4-3.

[21] M. Marcinkiewicz, N.G. Seidah, Coordinated expression of β-amyloid precursor protein and the putative β-secretase BACE and α-secretase ADAM10 in mouse and human brain, J. Neurochem. 75 (2000) 2133–2143, https://doi.org/10.1046/j.1471-4159.2000.0752133.x.

[22] H. Zheng, E.H. Koo, The amyloid precursor protein: beyond amyloid, Mol. Neurodegener. 1 (2006) 1–12, https://doi.org/10.1186/1750-1326-1-5.

[23] B. De Strooper, Loss-of-function presenilin mutations in Alzheimer disease. Talking point on the role of presenilin mutations in Alzheimer disease, EMBO Rep. 8 (2007) 141–146, https://doi.org/10.1038/sj.embor.7400897.

[24] S.S. Hébert, K. Horré, L. Nicolaï, B. Bergmans, A.S. Papadopoulou, A. Delacourte, B. De Strooper, MicroRNA regulation of Alzheimer's amyloid precursor protein expression, Neurobiol. Dis. 33 (2009) 422–428, https://doi.org/10.1016/j.nbd.2008.11.009.

[25] E. Vilardo, C. Barbato, M.T. Ciotti, C. Cogoni, F. Ruberti, MicroRNA-101 regulates amyloid precursor protein expression in hippocampal neurons, J. Biol. Chem. 285 (2010) 18344–18351, https://doi.org/10.1074/jbc.M110.112664.

[26] C.G. Liu, J. Song, Y.Q. Zhang, P.C. Wang, MicroRNA-193b is a regulator of amyloid precursor protein in the blood and cerebrospinal fluid derived exosomal microRNA-193b is a biomarker of Alzheimer's disease, Mol. Med. Rep. 10 (2014) 2395–2400, https://doi.org/10.3892/mmr.2014.2484.

[27] J.M. Long, B. Ray, 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. 287 (2012) 31298–31310, https://doi.org/10.1074/jbc.M112.366336.

[28] W. Liu, C. Liu, J. Zhu, P. Shu, B. Yin, Y. Gong, B. Qiang, J. Yuan, X. Peng, MicroRNA-16 targets amyloid precursor

protein to potentially modulate Alzheimer's-associated pathogenesis in SAMP8 mice, Neurobiol. Aging 33 (2012) 522–534, https://doi.org/10.1016/j.neurobiolaging.2010.04.034.
[29] P.L. Boutz, G. Chawla, P. Stoilov, D.L. Black, MicroRNAs regulate the expression of the alternative splicing factor nPTB during muscle development, Genes Dev. (2007), https://doi.org/10.1101/gad.1500707.
[30] E.V. Makeyev, J. Zhang, M.A. Carrasco, T. Maniatis, The microRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing, Mol. Cell (2007), https://doi.org/10.1016/j.molcel.2007.07.015.
[31] P. Smith, A. Al Hashimi, J. Girard, C. Delay, S.S. Hébert, In vivo regulation of amyloid precursor protein neuronal splicing by microRNAs, J. Neurochem. 116 (2011) 240–247, https://doi.org/10.1111/j.1471-4159.2010.07097.x.
[32] P.R. Manzine, S. Pelucchi, M.A. Horst, F.A.C. Vale, S.C.I. Pavarini, M. Audano, N. Mitro, M. Di Luca, E. Marcello, M.R. Cominetti, MicroRNA 221 targets ADAM10 mRNA and is downregulated in Alzheimer's disease, J. Alzheimers Dis. 61 (2018) 113–123, https://doi.org/10.3233/JAD-170592.
[33] C. Cheng, W. Li, Z. Zhang, S. Yoshimura, Q. Hao, C. Zhang, Z. Wang, MicroRNA-144 is regulated by activator protein-1 (AP-1) and decreases expression of Alzheimer disease-related a disintegrin and metalloprotease 10 (ADAM10), J. Biol. Chem. 288 (2013) 13748–13761, https://doi.org/10.1074/jbc.M112.381392.
[34] R. Akhter, Y. Shao, M. Shaw, S. Formica, M. Khrestian, J.B. Leverenz, L.M. Bekris, Regulation of ADAM10 by miR-140-5p and potential relevance for Alzheimer's disease, Neurobiol. Aging 63 (2018) 110–119, https://doi.org/10.1016/j.neurobiolaging.2017.11.007.
[35] S.S. Hebert, K. Horre, L. Nicolai, A.S. Papadopoulou, W. Mandemakers, A.N. Silahtaroglu, S. Kauppinen, A. Delacourte, B. De Strooper, Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/-secretase expression, Proc. Natl. Acad. Sci. 105 (2008) 6415–6420, https://doi.org/10.1073/pnas.0710263105.
[36] Y. Zong, H. Wang, W. Dong, X. Quan, H. Zhu, Y. Xu, L. Huang, C. Ma, C. Qin, miR-29c regulates BACE1 protein expression, Brain Res. 1395 (2011) 108–115, https://doi.org/10.1016/j.brainres.2011.04.035.
[37] W.-X. Wang, B.W. Rajeev, A.J. Stromberg, N. Ren, G. Tang, Q. Huang, I. Rigoutsos, P.T. Nelson, The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of β-site amyloid precursor protein-cleaving enzyme 1, J. Neurosci. (2008), https://doi.org/10.1523/JNEUROSCI.5065-07.2008.
[38] M. Fang, J. Wang, X. Zhang, Y. Geng, Z. Hu, J.A. Rudd, S. Ling, W. Chen, S. Han, The miR-124 regulates the expression of BACE1/β-secretase correlated with cell death in Alzheimer's disease, Toxicol. Lett. 209 (2012) 94–105, https://doi.org/10.1016/j.toxlet.2011.11.032.
[39] V. Boissonneault, I. Plante, S. Rivest, P. Provost, MicroRNA-298 and microRNA-328 regulate expression of mouse β-amyloid precursor protein-converting enzyme 1, J. Biol. Chem. 284 (2009) 1971–1981, https://doi.org/10.1074/jbc.M807530200.
[40] M. Faghihi, M. Zhang, J. Huang, F. Modarresi, M. Van der Brug, M. Nalls, M. Cookson, G. St-Laurent, C. Wahlestedt, Evidence for natural antisense transcript-mediated \ninhibition of microRNA function, Genome Biol (2010) 1–13.
[41] H.C. Zhu, L.M. Wang, M. Wang, B. Song, S. Tan, J.F. Teng, D.X. Duan, MicroRNA-195 downregulates Alzheimer's disease amyloid-β production by targeting BACE1, Brain Res. Bull. 88 (2012) 596–601, https://doi.org/10.1016/j.brainresbull.2012.05.018.
[42] J. Kim, J.M. Basak, D.M. Holtzman, The role of apolipoprotein E in Alzheimer's disease, Neuron 63 (2009) 287–303, https://doi.org/10.1016/j.neuron.2009.06.026.
[43] C. Lane-Donovan, J. Herz, ApoE, ApoE receptors, and the synapse in Alzheimer's disease, Trends Endocrinol. Metab. 28 (2017) 273–284, https://doi.org/10.1016/j.tem.2016.12.001.
[44] T. Kanekiyo, H. Xu, G. Bu, ApoE and Aβ in Alzheimer's disease: accidental encounters or partners? Neuron 81 (2014) 740–754, https://doi.org/10.1016/j.neuron.2014.01.045.
[45] J. Kim, H. Yoon, T. Horie, J.M. Burchett, J.L. Restivo, N. Rotllan, C.M. Ramirez, P.B. Verghese, M. Ihara, H.-S. Hoe, C. Esau, C. Fernandez-Hernando, D.M. Holtzman, J.R. Cirrito, K. Ono, J. Kim, microRNA-33 regulates ApoE lipidation and amyloid—metabolism in the brain, J. Neurosci. 35 (2015) 14717–14726, https://doi.org/10.1523/JNEUROSCI.2053-15.2015.
[46] W. Qin, T. Yang, L. Ho, Z. Zhao, J. Wang, L. Chen, W. Zhao, M. Thiyagarajan, D. MacGrogan, J.T. Rodgers, P. Puigserver, J. Sadoshima, H. Deng, S. Pedrini, S. Gandy, A.A. Sauve, G.M. Pasinetti, Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction, J. Biol. Chem. 281 (2006) 21745–21754, https://doi.org/10.1074/jbc.M602909200.
[47] S.W. Min, S.H. Cho, Y. Zhou, S. Schroeder, V. Haroutunian, W.W. Seeley, E.J. Huang, Y. Shen, E. Masliah, C. Mukherjee, D. Meyers, P.A. Cole, M. Ott, L. Gan, Acetylation of tau inhibits its degradation and contributes to tauopathy, Neuron 67 (2010) 953–966, https://doi.org/10.1016/j.neuron.2010.08.044.
[48] A. Hadar, E. Milanesi, M. Walczak, M. Puzianowska-Kuźnicka, J. Kuźnicki, A. Squassina, P. Niola, C. Chillotti, J. Attems, I. Gozes, D. Gurwitz, SIRT1, miR-132 and miR-212 link human longevity to Alzheimer's disease, Sci. Rep. 8 (2018) 1–10, https://doi.org/10.1038/s41598-018-26547-6.
[49] J. Gao, W.Y. Wang, Y.W. Mao, J. Gräff, J.S. Guan, L. Pan, G. Mak, D. Kim, S.C. Su, L.H. Tsai, A novel pathway regulates memory and plasticity via SIRT1 and miR-134, Nature 466 (2010) 1105–1109, https://doi.org/10.1038/nature09271.
[50] Y. Zhao, X. Wu, X. Li, L.L. Jiang, X. Gui, Y. Liu, Y. Sun, B. Zhu, J.C. Piña-Crespo, M. Zhang, N. Zhang, X. Chen, G. Bu, Z. An, T.Y. Huang, H. Xu, TREM2 is a receptor for β-amyloid that mediates microglial function, Neuron 97 (2018) 1023–1031.e7, https://doi.org/10.1016/j.neuron.2018.01.031.
[51] Y. Zhao, S. Bhattacharjee, B.M. Jones, P. Dua, P.N. Alexandrov, J.M. Hill, W.J. Lukiw, Regulation of TREM2 expression by an NF-kB-sensitive miRNA-34a, Neuroreport 24 (2013) 318–323, https://doi.org/10.1097/WNR.0b013e32835fb6b0.
[52] Y. Zhao, V. Jaber, 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. 8 (2016) 1–5, https://doi.org/10.3389/fnagi.2016.00140.
[53] A. Freischmidt, K. Müller, A.C. Ludolph, J.H. Weishaupt, Systemic dysregulation of TDP-43 binding microRNAs in amyotrophic lateral sclerosis, Acta Neuropathol. Commun. 1 (2013) 42, https://doi.org/10.1186/2051-5960-1-42.
[54] M. Polymenidou, C. Lagier-Tourenne, K.R. Hutt, S.C. Huelga, J. Moran, T.Y. Liang, S.C. Ling, E. Sun, E. Wancewicz, C.

Mazur, H. Kordasiewicz, Y. Sedaghat, J.P. Donohue, L. Shiue, C.F. Bennett, G.W. Yeo, D.W. Cleveland, Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43, Nat. Neurosci. 14 (2011) 459–468, https://doi.org/10.1038/nn.2779.

[55] Z. Zhang, S. Almeida, Y. Lu, A.L. Nishimura, L. Peng, D. Sun, B. Wu, A.M. Karydas, M.C. Tartaglia, J.C. Fong, B.L. Miller, R.V. Farese, M.J. Moore, C.E. Shaw, F.B. Gao, Downregulation of microRNA-9 in iPSC-derived neurons of FTD/ALS patients with TDP-43 mutations, PLoS One 8 (2013), https://doi.org/10.1371/journal.pone.0076055.

[56] S.-E. Sim, C.-S. Lim, J.-I. Kim, D. Seo, H. Chun, N.-K. Yu, J. Lee, S.J. Kang, H.-G. Ko, J.-H. Choi, T. Kim, E.-H. Jang, J. Han, M.S. Bak, J.-E. Park, D.-J. Jang, D. Baek, Y.-S. Lee, B.-K. Kaang, The brain-enriched microRNA miR-9-3p regulates synaptic plasticity and memory, J. Neurosci. 36 (2016) 8641–8652, https://doi.org/10.1523/JNEUROSCI.0630-16.2016.

[57] T.L. Petkau, B.R. Leavitt, Progranulin in neurodegenerative disease, Trends Neurosci. 37 (2014) 388–398, https://doi.org/10.1016/j.tins.2014.04.003.

[58] M.C. Chang, K. Srinivasan, B.A. Friedman, E. Suto, Z. Modrusan, W.P. Lee, J.S. Kaminker, D.V. Hansen, M. Sheng, Progranulin deficiency causes impairment of autophagy and TDP-43 accumulation, J. Exp. Med. 214 (2017) 2611–2628, https://doi.org/10.1084/jem.20160999.

[59] A.E. Arrant, V.C. Onyilo, D.E. Unger, E.D. Roberson, Progranulin gene therapy improves lysosomal dysfunction and microglial pathology associated with frontotemporal dementia and neuronal ceroid lipofuscinosis, J. Neurosci. 38 (2018) 3081-17, https://doi.org/10.1523/JNEUROSCI.3081-17.2018.

[60] J. Kocerha, N. Kouri, M. Baker, N. Finch, M. DeJesus-Hernandez, J. Gonzalez, K. Chidamparam, K.A. Josephs, B.F. Boeve, N.R. Graff-Radford, J. Crook, D.W. Dickson, R. Rademakers, Altered microRNA expression in frontotemporal lobar degeneration with TDP-43 pathology caused by progranulin mutations, BMC Genomics 12 (2011), https://doi.org/10.1186/1471-2164-12-527.

[61] K. Iqbal, F. Liu, C.X. Gong, Tau and neurodegenerative disease: the story so far, Nat. Rev. Neurol. 12 (2016) 15–27, https://doi.org/10.1038/nrneurol.2015.225.

[62] Y. Wang, E. Mandelkow, Tau in physiology and pathology, Nat. Rev. Neurosci. 17 (2016) 5–21, https://doi.org/10.1038/nrn.2015.1.

[63] A.D. Alonso, I. Grundke-Iqbal, H.S. Barra, K. Iqbal, Abnormal phosphorylation of tau and the mechanism of Alzheimer neurofibrillary degeneration: sequestration of microtubule-associated proteins 1 and 2 and the disassembly of microtubules by the abnormal tau, PNAS (1997), https://doi.org/10.1073/pnas.94.1.298.

[64] K. Iqbal, A.D.C. Alonso, I. Grundke-Iqbal, Cytosolic abnormally hyperphosphorylated tau but not paired helical filaments sequester normal MAPs and inhibit microtubule assembly, J. Alzheimers Dis. (2008), https://doi.org/10.3233/JAD-2008-14402.

[65] P. Lau, K. Bossers, R. Janky, E. Salta, C.S. Frigerio, S. Barbash, R. Rothman, A.S.R. Sierksma, A. Thathiah, D. Greenberg, A.S. Papadopoulou, T. Achsel, T. Ayoubi, H. Soreq, J. Verhaagen, D.F. Swaab, S. Aerts, B. De Strooper, Alteration of the microRNA network during the progression of Alzheimer's disease, EMBO Mol. Med. 5 (2013) 1613–1634, https://doi.org/10.1002/emmm.201201974.

[66] Q. Bin Zhu, U. Unmehopa, K. Bossers, Y.T. Hu, R. Verwer, R. Balesar, J. Zhao, A.M. Bao, D. Swaab, MicroRNA-132 and early growth response-1 in nucleus basalis of Meynert during the course of Alzheimer's disease, Brain 139 (2016) 908–921, https://doi.org/10.1093/brain/awv383.

[67] S. Absalon, D.M. Kochanek, V. Raghavan, A.M. Krichevsky, MiR-26b, upregulated in Alzheimer's disease, activates cell cycle entry, tau-phosphorylation, and apoptosis in postmitotic neurons, J. Neurosci. 33 (2013) 14645–14659, https://doi.org/10.1523/JNEUROSCI.1327-13.2013.

[68] X. Wang, L. Tan, Y. Lu, J. Peng, Y. Zhu, Y. Zhang, Z. Sun, MicroRNA-138 promotes tau phosphorylation by targeting retinoic acid receptor alpha, FEBS Lett. 589 (2015) 726–729, https://doi.org/10.1016/j.febslet.2015.02.001.

[69] M.B. Goncalves, E. Clarke, C. Hobbs, T. Malmqvist, R. Deacon, J. Jack, J.P.T. Corcoran, Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by an retinoic acid receptor α agonist, Eur. J. Neurosci. 37 (2013) 1182–1192, https://doi.org/10.1111/ejn.12142.

[70] S. Sharma, I. Khadimallah, A.W. Corya, Y.O. Ali, X. Rao, Y. Liu, H.-C. Lu, Presymptomatic change in microRNAs modulates Tau pathology, Sci. Rep. 8 (2018), 9251. https://doi.org/10.1038/s41598-018-27527-6.

[71] P. Li, J. Jiao, G. Gao, B.S. Prabhakar, Control of mitochondrial activity by miRNAs, J. Cell. Biochem. (2012), https://doi.org/10.1016/j.carbpol.2015.04.023.

[72] P.I. Moreira, C. Carvalho, X. Zhu, M.A. Smith, G. Perry, Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology, Biochim. Biophys. Acta Mol. basis Dis. 1802 (2010) 2–10, https://doi.org/10.1016/j.bbadis.2009.10.006.

[73] Q. Ding, W.R. Markesbery, V. Cecarini, J.N. Keller, Decreased RNA, and increased RNA oxidation, in ribosomes from early Alzheimer's disease, Neurochem. Res. 31 (2006) 705–710, https://doi.org/10.1007/s11064-006-9071-5.

[74] Q. Kong, C.L.G. Lin, Oxidative damage to RNA: mechanisms, consequences, and diseases, Cell. Mol. Life Sci. (2010), https://doi.org/10.1007/s00018-010-0277-y.

[75] A. Aschrafi, A.D. Schwechter, M.G. Mameza, O. Natera-Naranjo, A.E. Gioio, B.B. Kaplan, MicroRNA-338 regulates local cytochrome c oxidase IV mRNA levels and oxidative phosphorylation in the axons of sympathetic neurons, J. Neurosci. 28 (2008) 12581–12590, https://doi.org/10.1523/JNEUROSCI.3338-08.2008.

[76] P. Gao, I. Tchernyshyov, T.C. Chang, Y.S. Lee, K. Kita, T. Ochi, K.I. Zeller, A.M. De Marzo, J.E. Van Eyk, J.T. Mendell, C.V. Dang, C-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism, Nature 458 (2009) 762–765, https://doi.org/10.1038/nature07823.

[77] A. Cimmino, G.A. Calin, M. Fabbri, M.V. Iorio, M. Ferracin, M. Shimizu, S.E. Wojcik, R.I. Aqeilan, S. Zupo, M. Dono, L. Rassenti, H. Alder, S. Volinia, C.-g. Liu, T.J. Kipps, M. Negrini, C.M. Croce, miR-15 and miR-16 induce apoptosis by targeting BCL2, Proc. Natl. Acad. Sci. 102 (2005) 13944–13949, https://doi.org/10.1073/pnas.0506654102.

[78] J. Li, S. Donath, Y. Li, D. Qin, B.S. Prabhakar, P. Li, miR-30 regulates mitochondrial fission through targeting p53 and the dynamin-related protein-1 pathway, PLoS Genet. 6 (2010), https://doi.org/10.1371/journal.pgen.1000795.

[79] R. Zhang, H. Zhou, L. Jiang, Y. Mao, X. Cui, B. Xie, D. Cui, H. Wang, Q. Zhang, S. Xu, MiR-195 dependent roles of mitofusin2 in the mitochondrial dysfunction of hippocampal neurons in SAMP8 mice, Brain Res. 1652 (2016) 135–143, https://doi.org/10.1016/j.brainres.2016.09.047.

[80] G. Santulli, F.M. Biology, microRNA : Basic Science, 2015.
[81] C.L. Kragh, K. Ubhi, T. Wyss-Corey, E. Masliah, Autophagy in dementias, Brain Pathol. 22 (2012) 99–109, https://doi.org/10.1111/j.1750-3639.2011.00545.x.
[82] M.M. Lipinski, B. Zheng, T. Lu, Z. Yan, B.F. Py, A. Ng, R.J. Xavier, C. Li, B.A. Yankner, C.R. Scherzer, J. Yuan, Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease, Proc. Natl. Acad. Sci. 107 (2010) 14164–14169, https://doi.org/10.1073/pnas.1009485107.
[83] D.S. Yang, P. Stavrides, P.S. Mohan, S. Kaushik, A. Kumar, M. Ohno, S.D. Schmidt, D. Wesson, U. Bandyopadhyay, Y. Jiang, M. Pawlik, C.M. Peterhoff, A.J. Yang, D.A. Wilson, P. St George-Hyslop, D. Westaway, P.M. Mathews, E. Levy, A.M. Cuervo, R.A. Nixon, Reversal of autophagy dysfunction in the TgCRND8 mouse model of Alzheimer's disease ameliorates amyloid pathologies and memory deficits, Brain 134 (2011) 258–277, https://doi.org/10.1093/brain/awq341.
[84] X. Zhang, K. Garbett, K. Veeraraghavalu, B. Wilburn, R. Gilmore, K. Mirnics, S.S. Sisodia, A role for presenilins in autophagy revisited: normal acidification of lysosomes in cells lacking PSEN1 and PSEN2, J. Neurosci. (2012), https://doi.org/10.1523/JNEUROSCI.0556-12.2012.
[85] K.M. Neely, K.N. Green, F.M. LaFerla, Presenilin is necessary for efficient proteolysis through the autophagy–lysosome system in a γ-secretase-independent manner, J. Neurosci. 31 (2011) 2781–2791, https://doi.org/10.1523/JNEUROSCI.5156-10.2010.
[86] R. Dobrowolski, P. Vick, D. Ploper, I. Gumper, H. Snitkin, D. D. Sabatini, E.M. De Robertis, Presenilin deficiency or lysosomal inhibition enhances Wnt signaling through relocalization of GSK3 to the late-endosomal compartment, Cell Rep. 2 (2012) 1316–1328, https://doi.org/10.1016/j.celrep.2012.09.026.
[87] C.A. Wilson, D.D. Murphy, B.I. Giasson, B. Zhang, J.Q. Trojanowski, V.M.Y. Lee, Degradative organelles containing mislocalized α- and β-synuclein proliferate in presenilin-1 null neurons, J. Cell Biol. 165 (2004) 335–346, https://doi.org/10.1083/jcb.200403061.
[88] G. Esselens, V. Oorschot, V. Baert, T. Raemaekers, K. Spittaels, L. Serneels, H. Zheng, P. Saftig, B. De Strooper, J. Klumperman, W. Annaert, Presenilin 1 mediates the turnover of telencephalin in hippocampal neurons via an autophagic degradative pathway, J. Cell Biol. 166 (2004) 1041–1054, https://doi.org/10.1083/jcb.200406060.
[89] J.H. Lee, W.H. Yu, A. Kumar, S. Lee, P.S. Mohan, C.M. Peterhoff, D.M. Wolfe, M. Martinez-Vicente, A.C. Massey, G. Sovak, Y. Uchiyama, D. Westaway, A.M. Cuervo, R.A. Nixon, Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations, Cell 141 (2010) 1146–1158, https://doi.org/10.1016/j.cell.2010.05.008.
[90] C. LIANG, yongfei yang, MicroRNAs: an emerging player in autophagy, Sci. Res. (2014), https://doi.org/10.14293/S2199-1006.1.SOR-LIFE.A181CU.v1.
[91] Y. Zhang, C. Liu, J. Wang, Q. Li, H. Ping, S. Gao, P. Wang, MIR-299-5p regulates apoptosis through autophagy in neurons and ameliorates cognitive capacity in APPswe/PS1dE9 mice, Sci. Rep. 6 (2016) 1–14, https://doi.org/10.1038/srep24566.
[92] J. Sun, X. Gao, D. Meng, Y. Xu, X. Wang, X. Gu, M. Guo, X. Shao, H. Yan, C. Jiang, Y. Zheng, Antagomirs targeting MiroRNA-134 attenuates epilepsy in rats through regulation of oxidative stress, mitochondrial functions and autophagy, Front. Pharmacol. 8 (2017) 1–9, https://doi.org/10.3389/fphar.2017.00524.
[93] D. Gibbings, S. Mostowy, O. Voinnet, Autophagy selectively regulates miRNA homeostasis, Autophagy 9 (2013) 781–783, https://doi.org/10.4161/auto.23694.
[94] W. Springer, P.J. Kahle, Regulation of PINK1–Parkin-mediated mitophagy, Autophagy 7 (2011) 266–278, https://doi.org/10.4161/auto.7.3.14348.
[95] M. Cheng, L. Liu, Y. Lao, W. Liao, M. Liao, X. Luo, J. Wu, W. Xie, Y. Zhang, N. Xu, MicroRNA-181a suppresses parkin-mediated mitophagy and sensitizes neuroblastoma cells to mitochondrial uncoupler-induced apoptosis, Oncotarget 7 (2016) 42274–42287, https://doi.org/10.18632/oncotarget.9786.
[96] J. Kim, F.C. Fiesel, K.C. Belmonte, R. Hudec, W.X. Wang, C. Kim, P.T. Nelson, W. Springer, J. Kim, MiR-27a and miR-27b regulate autophagic clearance of damaged mitochondria by targeting PTEN-induced putative kinase 1 (PINK1), Mol. Neurodegener. 11 (2016), https://doi.org/10.1186/s13024-016-0121-4.
[97] J.E. Cohen, P.R. Lee, S. Chen, W. Li, R.D. Fields, MicroRNA regulation of homeostatic synaptic plasticity, Proc. Natl. Acad. Sci. 108 (2011) 11650–11655, https://doi.org/10.1073/pnas.1017576108.
[98] D. Kabogo, G. Rauw, A. Amritraj, G. Baker, S. Kar, β-Amyloid-related peptides potentiate K+-evoked glutamate release from adult rat hippocampal slices, Neurobiol. Aging 31 (2010) 1164–1172, https://doi.org/10.1016/j.neurobiolaging.2008.08.009.
[99] E. Abramov, I. Dolev, H. Fogel, G.D. Ciccotosto, E. Ruff, I. Slutsky, Amyloid-beta as a positive endogenous regulator of release probability at hippocampal synapses, Nat. Neurosci. 12 (2009), https://doi.org/10.1038/nn.2433.
[100] J. Park, M. Jang, S. Chang, Neurobiology of disease deleterious effects of soluble amyloid-β oligomers on multiple steps of synaptic vesicle trafficking, Neurobiol. Dis. 55 (2013) 129–139, https://doi.org/10.1016/j.nbd.2013.03.004.
[101] K. Parameshwaran, M. Dhanasekaran, V. Suppiramaniam, Amyloid beta peptides and glutamatergic synaptic dysregulation, Exp. Neurol. 210 (2008) 7–13, https://doi.org/10.1016/j.expneurol.2007.10.008.
[102] S. Li, M. Jin, T. Koeglsperger, N.E. Shepardson, G.M. Shankar, D.J. Selkoe, Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors, J. Neurosci 31 (2011) 6627–6638, https://doi.org/10.1523/JNEUROSCI.0203-11.2011.
[103] E. Alberdi, M.V. Sánchez-gómez, F. Cavaliere, A. Pérez-samartín, J. Luis, R. Trullas, M. Domercq, C. Matute, Amyloid β oligomers induce Ca^{2+} dysregulation and neuronal death through activation of ionotropic glutamate receptors, Cell Calcium 47 (2010) 264–272, https://doi.org/10.1016/j.ceca.2009.12.010.
[104] G.M. Shankar, B.L. Bloodgood, M. Townsend, D.M. Walsh, D.J. Selkoe, B.L. Sabatini, Natural oligomers of the Alzheimer amyloid-β protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway, J. Neurosci 27 (2007) 2866–2875, https://doi.org/10.1523/JNEUROSCI.4970-06.2007.
[105] L.P. Mark, R.W. Prost, J.L. Ulmer, M.M. Smith, D.L. Daniels, J.M. Strottmann, W.D. Brown, L. Hacein-bey, Pictorial review of glutamate excitotoxicity : fundamental concepts for neuroimaging, AJNR Am. J. Neuroradiol (2001) 1813–1824.

[106] Z. Hu, J. Zhao, T. Hu, Y. Luo, J. Zhu, Z. Li, miR-501-3p mediates the activity-dependent regulation of the expression of AMPA receptor subunit GluA1, J. Cell Biol 208 (2007) 949–959, https://doi.org/10.1083/jcb.201404092.

[107] M. Letellier, S. Elramah, M. Mondin, A. Soula, A. Penn, D. Choquet, M. Landry, O. Thoumine, A. Favereaux, miR-92a regulates expression of synaptic GluA1-containing AMPA receptors during homeostatic scaling, Nat. Neurosci (2014) 13–16, https://doi.org/10.1038/nn.3762.

[108] R. Saba, P.H. Störchel, A. Aksoy-aksel, F. Kepura, G. Lippi, T.D. Plant, G.M. Schratt, Dopamine-regulated microRNA MiR-181a controls GluA2 surface expression in hippocampal neurons, Mol. Cell Biol. (2012) 619–632, https://doi.org/10.1128/MCB.05896-11.

[109] M.M. Harraz, S.M. Eacker, X. Wang, T.M. Dawson, V.L. Dawson, MicroRNA-223 is neuroprotective by targeting glutamate receptors, Proc. Natl. Acad. Sci. U. S. A. (2012) 2–7, https://doi.org/10.1073/pnas.1121288109/–/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1121288109.

[110] V.M. Ho, L.O. Dallalzadeh, N. Karathanasis, M.F. Keles, S. Vangala, T. Grogan, P. Poirazi, K.C. Martin, GluA2 mRNA distribution and regulation by miR-124 in hippocampal neurons, Mol. Cell. Neurosci. (2014), https://doi.org/10.1016/j.mcn.2014.04.006.

[111] H. Shen, Z. Li, miRNAs in NMDA receptor-dependent synaptic plasticity and psychiatric disorders, Clin. Sci. (Lond.) 130 (2016) 1137–1146, https://doi.org/10.1042/CS20160046.

[112] S.S. Aw, I. Kok, H. Lim, M. Xue, M. Tang, S.S. Aw, I. Kok, H. Lim, M. Xue, M. Tang, S.M. Cohen, A glio-protective role of mir-263a by tuning sensitivity to glutamate, Cell Rep. 19 (2017) 1783–1793, https://doi.org/10.1016/j.celrep.2017.05.010.

[113] H. Scott, J. Howarth, Y.B. Lee, L.F. Wong, I. Bantounas, L. Phylactou, P. Verkade, J.B. Uney, MiR-3120 is a mirror microRNA that targets heat shock cognate protein 70 and auxilin messenger RNAs and regulates clathrin vesicle uncoating, J. Biol. Chem. 287 (2012) 14726–14733, https://doi.org/10.1074/jbc.M111.326041.

[114] J.F. Aranda, A. Canfran-Duque, L. Goedeke, Y. Suarez, C. Fernandez-Hernando, The miR-199–dynamin regulatory axis controls receptor-mediated endocytosis, J. Cell Sci. 128 (2015) 3197–3209, https://doi.org/10.1242/jcs.165233.

[115] G. Davidkova, R.C. Carroll, Characterization of the role of microtubule-associated protein 1B in metabotropic glutamate receptor-mediated endocytosis of AMPA receptors in hippocampus, J. Neurosci. 27 (2007) 13273–13278, https://doi.org/10.1523/JNEUROSCI.3334-07.2007.

[116] S. Chowdhury, J.D. Shepherd, H. Okuno, G. Lyford, R.S. Petralia, N. Plath, D. Kuhl, R.L. Huganir, P.F. Worley, Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking, Neuron (2006), https://doi.org/10.1016/j.jhazmat.2009.08.026.

[117] M. Benoist, R. Palenzuela, C. Rozas, P. Rojas, E. Tortosa, B. Morales, C. González-Billault, J. Ávila, J.A. Esteban, MAP1B-dependent Rac activation is required for AMPA receptor endocytosis during long-term depression, EMBO J. (2013), https://doi.org/10.1038/emboj.2013.166.

[118] Y.-L. Chen, C.-K.J. Shen, Modulation of mGluR-dependent MAP1B translation and AMPA receptor endocytosis by microRNA miR-146a-5p, J. Neurosci. 33 (2013) 9013–9020, https://doi.org/10.1523/JNEUROSCI.5210-12.2013.

[119] Y. Ye, H. Xu, X. Su, X. He, Role of microRNA in governing synaptic plasticity, Neural Plast. 2016 (2016), https://doi.org/10.1155/2016/4959523.

[120] P. Verma, G.J. Augustine, M.R. Ammar, A. Tashiro, S.M. Cohen, A neuroprotective role for microRNA miR-1000 mediated by limiting glutamate excitotoxicity, Nat. Neurosci. 18 (2015) 379–387, https://doi.org/10.1038/nn.3935.

[121] V.Y. Poon, M. Gu, F. Ji, A.M. VanDongen, M. Fivaz, miR-27b shapes the presynaptic transcriptome and influences neurotransmission by silencing the polycomb group protein Bmi1, BMC Genomics 17 (2016) 1–14, https://doi.org/10.1186/s12864-016-3139-7.

[122] P.J. Yao, M. Zhu, E.I. Pyun, A.I. Brooks, S. Therianos, V.E. Meyers, P.D. Coleman, Defects in expression of genes related to synaptic vesicle trafficking in frontal cortex of Alzheimer's disease, Neurobiol. Dis. 12 (2003) 97–109, https://doi.org/10.1016/S0969-9961(02)00009-8.

[123] L. Morel, M. Regan, H. Higashimori, S.K. Ng, C. Esau, S. Vidensky, J. Rothstein, Y. Yang, Neuronal exosomal miRNA-dependent translational regulation of astroglial glutamate transporter GLT1, 288 (2013) 7105–7116, https://doi.org/10.1074/jbc.M112.410944.

[124] C. Lafourcade, J.P. Ramírez, A. Luarte, A. Fernández, U. Wyneken, MiRNAs in astrocyte-derived exosomes as possible mediators of neuronal plasticity, J. Exp. Neurosci 10 (2016) 1–9, https://doi.org/10.4137/JEN.S39916.TYPE.

[125] T. Lashley, J.M. Schott, P. Weston, C.E. Murray, H. Wellington, A. Keshavan, S.C. Foti, M. Foiani, J. Toombs, J.D. Rohrer, A. Heslegrave, H. Zetterberg, Molecular biomarkers of Alzheimer's disease: progress and prospects, Dis. Model. Mech. 11 (2018), dmm031781. https://doi.org/10.1242/dmm.031781.

[126] E. Tönnies, E. Trushina, Oxidative stress, synaptic dysfunction, and Alzheimer's disease, J. Alzheimers Dis. 57 (2017) 1105–1121, https://doi.org/10.3233/JAD-161088.

[127] V.M. Ho, J.A. Lee, K.C. Martin, The cell biology of synaptic plasticity, Science (2011), https://doi.org/10.1126/science.1209236.

[128] C. Hanus, E.M. Schuman, Proteostasis in complex dendrites, Nat. Rev. Neurosci. 14 (2013) 638–648, https://doi.org/10.1038/nrn3546.

[129] Y. Nakahata, R. Yasuda, Plasticity of spine structure: local signaling, translation and cytoskeletal reorganization, Front. Synaptic Neurosci. 10 (2018) 1–13, https://doi.org/10.3389/fnsyn.2018.00029.

[130] F. Ahmad, K. Singh, D. Das, R. Gowaikar, E. Shaw, A. Ramachandran, K.V. Rupanagudi, R.P. Kommaddi, D.A. Bennett, V. Ravindranath, Reactive oxygen species-mediated loss of synaptic Akt1 signaling leads to deficient activity-dependent protein translation early in Alzheimer's disease, Antioxid. Redox Signal. 27 (2017) 1269–1280, https://doi.org/10.1089/ars.2016.6860.

[131] T. Ma, M.A. Trinh, A.J. Wexler, C. Bourbon, E. Gatti, P. Pierre, D.R. Cavener, E. Klann, Suppression of eIF2α kinases alleviates Alzheimer's disease-related plasticity and memory deficits, Nat. Neurosci. 16 (2013) 1299–1305, https://doi.org/10.1038/nn.3486.

[132] Z. Hu, Z. Li, miRNAs in synapse development and synaptic plasticity, Curr. Opin. Neurobiol. (2017), https://doi.org/10.1016/j.conb.2017.02.014.

[133] G. Siegel, R. Saba, G. Schratt, MicroRNAs in neurons: manifold regulatory roles at the synapse, Curr. Opin. Genet. Dev. 21 (2011) 491–497, https://doi.org/10.1016/j.gde.2011.04.008.

[134] G.M. Schratt, F. Tuebing, E.A. Nigh, C.G. Kane, M.E. Sabatini, M. Kiebler, M.E. Greenberg, A brain-specific microRNA regulates dendritic spine development, Nature 439 (2006) 283–289, https://doi.org/10.1038/nature04367.

[135] G. Siegel, G. Obernosterer, R. Fiore, M. Oehmen, S. Bicker, M. Christensen, S. Khudayberdiev, P.F. Leuschner, C.J.L. Busch, C. Kane, K. Hübel, F. Dekker, C. Hedberg, B. Rengarajan, C. Drepper, H. Waldmann, S. Kauppinen, M.E. Greenberg, A. Draguhn, M. Rehmsmeier, J. Martinez, G.M. Schratt, A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis, Nat. Cell Biol. 11 (2009) 705–716, https://doi.org/10.1038/ncb1876.

[136] S. Bicker, M. Lackinger, K. Weiß, G. Schratt, MicroRNA-132, -134, and -138: a microRNA troika rules in neuronal dendrites, Cell. Mol. Life Sci. 71 (2014) 3987–4005, https://doi.org/10.1007/s00018-014-1671-7.

[137] D. Edbauer, J.R. Neilson, K.A. Foster, C.F. Wang, D.P. Seeburg, M.N. Batterton, T. Tada, B.M. Dolan, P.A. Sharp, M. Sheng, Regulation of synaptic structure and function by FMRP-associated microRNAs miR-125b and miR-132, Neuron (2010), https://doi.org/10.1016/j.neuron.2010.01.005.

[138] J.Y. Yu, K.H. Chung, M. Deo, R.C. Thompson, D.L. Turner, MicroRNA miR-124 regulates neurite outgrowth during neuronal differentiation, Exp. Cell Res. (2008), https://doi.org/10.1016/j.yexcr.2008.06.002.

[139] A.X. Sun, G.R. Crabtree, A.S. Yoo, MicroRNAs: regulators of neuronal fate, Curr. Opin. Cell Biol. (2013), https://doi.org/10.1016/j.ceb.2012.12.007.

[140] E. Gascon, K. Lynch, H. Ruan, S. Almeida, J.M. Verheyden, W.W. Seeley, D.W. Dickson, L. Petrucelli, D. Sun, J. Jiao, H. Zhou, M. Jakovcevski, S. Akbarian, W.D. Yao, F.B. Gao, Alterations in microRNA-124 and AMPA receptors contribute to social behavioral deficits in frontotemporal dementia, Nat. Med. (2014), https://doi.org/10.1038/nm.3717.

[141] A.E. Arrant, E.D. Roberson, MicroRNA-124 modulates social behavior in frontotemporal dementia, Nat. Med. 20 (2014) 1381–1383, https://doi.org/10.1038/nm.3768.

[142] F. Zampa, S. Bicker, G. Schratt, Activity-dependent pre-miR-134 dendritic localization is required for hippocampal neuron dendritogenesis, Front. Mol. Neurosci. 11 (2018) 1–14, https://doi.org/10.3389/fnmol.2018.00171.

[143] S. Sambandan, G. Akbalik, L. Kochen, J. Rinne, J. Kahlstatt, C. Glock, G. Tushev, B. Alvarez-Castelao, A. Heckel, E.M. Schuman, Activity-dependent spatially localized miRNA maturation in neuronal dendrites, Science 355 (2017) 634–637, https://doi.org/10.1126/science.aaf8995.

[144] M. Zendjabil, Circulating microRNAs as novel biomarkers of Alzheimer's disease, Clin. Chim. Acta 484 (2018) 99–104, https://doi.org/10.1016/j.cca.2018.05.039.

[145] K. Burgos, I. Malenica, R. Metpally, A. Courtright, B. Rakela, T. Beach, H. Shill, C. Adler, M. Sabbagh, S. Villa, W. Tembe, D. Craig, K. Van Keuren-Jensen, Profiles of extracellular miRNA in cerebrospinal fluid and serum from patients with Alzheimer's and Parkinson's diseases correlate with disease status and features of pathology, PLoS One 9 (2014), https://doi.org/10.1371/journal.pone.0094839.

[146] H. Geekiyanage, G.A. Jicha, P.T. Nelson, C. Chan, Blood serum miRNA: non-invasive biomarkers for Alzheimer's disease, Exp. Neurol. 235 (2012) 491–496, https://doi.org/10.1016/j.expneurol.2011.11.026.

[147] H.Z.Y. Wu, K.L. Ong, K. Seeher, N.J. Armstrong, A. Thalamuthu, H. Brodaty, P. Sachdev, K. Mather, Circulating microRNAs as biomarkers of Alzheimer's disease: a systematic review, J. Alzheimers Dis. 49 (2016) 755–766, https://doi.org/10.3233/JAD-150619.

[148] S. Kumar, P.H. Reddy, Are circulating microRNAs peripheral biomarkers for Alzheimer's disease? Biochim. Biophys. Acta Mol. basis Dis. 1862 (2016) 1617–1627, https://doi.org/10.1016/j.bbadis.2016.06.001.