NeuroMolecular Medicine (2019) 21:369–390
https://doi.org/10.1007/s12017-019-08568-0

REVIEW PAPER

Cerebral Amyloid Angiopathy, Alzheimer's Disease and MicroRNA: miRNA as Diagnostic Biomarkers and Potential Therapeutic Targets

J. Weldon Furr[1] · Diego Morales-Scheihing[1] · Bharti Manwani[1] · Juneyoung Lee[1] · Louise D. McCullough[1]

Received: 12 June 2019 / Accepted: 4 September 2019 / Published online: 4 October 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

The protein molecules must fold into unique conformations to acquire functional activity. Misfolding, aggregation, and deposition of proteins in diverse organs, the so-called "protein misfolding disorders (PMDs)", represent the conformational diseases with highly ordered assemblies, including oligomers and fibrils that are linked to neurodegeneration in brain illnesses such as cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD). Recent studies have revealed several aspects of brain pathology in CAA and AD, but both the classification and underlying mechanisms need to be further refined. MicroRNAs (miRNAs) are critical regulators of gene expression at the post-transcriptional level. Increasing evidence with the advent of RNA sequencing technology suggests possible links between miRNAs and these neurodegenerative disorders. To provide insights on the small RNA-mediated regulatory circuitry and the translational significance of miRNAs in PMDs, this review will discuss the characteristics and mechanisms of the diseases and summarize circulating or tissue-resident miRNAs associated with AD and CAA.

Keywords Alzheimer's disease · Cerebral amyloid angiopathy · Intracerebral hemorrhage · MicroRNA · Protein misfolding

Protein Misfolding Disorders

Protein misfolding disorders (PMDs) are a group of pathologies characterized by the deposition of aggregated misfolded protein in diverse organs (Soto et al. 2006). Several studies have demonstrated that the accumulation of misfolded protein in tissues causes injury and that this is a signature characteristic of these diseases (Soto et al. 2006). PMDs include a variety of neurodegenerative diseases including Alzheimer's disease (AD), cerebral amyloid angiopathy (CAA), prion diseases (also known as transmissible spongiform encephalopathies), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). PMDs also occur in many other non-brain related disorders, such as systemic amyloidosis, type 2 diabetes (T2D) (Mukherjee et al. 2017), and familial amyloid polyneuropathy, among others (Soto 2003; Mukherjee et al. 2015) (Table 1).

The financial burden of these diseases has steadily increased due to the aging of the general population (Association 2019). Studies have shown that today, 5 million Americans suffer from AD (Association 2019); 1 million from PD (Marras et al. 2018); 30,000 from ALS (Petrov et al. 2017), and 30,000 from HD (Mullard 2019), and these numbers will continue to grow.

Studies have shown that environmental conditions (pH, temperature, and ionic strength), and protein concentration are the major factors triggering protein misfolding, which is accumulated in amyloid plaques in different diseases (Fink 1998). In general, the mechanism of protein misfolding is the transition of a normal protein (which is mainly random coil or α-helical structures) into β-sheets by a seeding-nucleation model. This can be divided into two different kinetic phases. The first phase is called the lag phase. During this phase, misfolding of soluble monomeric species and formation of small β-structures called oligomers takes place. Once stable nuclei (oligomers) are formed, there is a second phase of elongation. β-structures interact with each other, mainly through hydrogen bonds, resulting in the rapid growth of oligomers into a very stable structure consisting of insoluble fibrils (Chiti and Dobson 2017). Amyloid plaques are depositions of misfolded insoluble material, which are disease specific (Chiti and Dobson 2017). Of the amyloid proteins found in plaques, amyloid-β is found in AD and CAA,

✉ Louise D. McCullough
Louise.D.McCullough@uth.tmc.edu

[1] BRAINS Research Laboratory, University of Texas McGovern Medical School, Houston, TX 77030, USA

Table 1 A collection of various forms of protein misfolding disorders, including the protein of interest, the diseased organ, and the clinical presentation of each disease

Protein misfolding disorders				
Disorder	Protein	Organ	Clinical feature	References
Creutzfeld–Jakob disease	Prion protein	Brain	Dementia, ataxia, psychiatric problems or insomnia	Prusiner (1982, 1998)
Huntington's disease	Huntington	Brain	Movement disorder	Williams et al. (2008) and Tsoi et al. (2012)
Alzheimer's disease	Amyloid-β and tau	Brain	Dementia, motor, and psychiatric problems	Hardy and Selkoe (2002) and Dobson (1999)
Parkinson's disease	α-Synuclein	Brain	Movement disorder	Martin et al. (2011) and Uversky (2007)
Amyotrophic lateral sclerosis	Superoxide dismutase	Brain	Motor and movement disorder	Andersen and Al-Chalabi (2011)
Type II diabetes	Islet amyloid polypeptide	Pancreas	Hormonal disorder	Akter et al. (2016) and Westermark et al. (2011)
AA amyloidosis	Serum amyloid A	Multiple organs	Varying symptoms depending on where the amyloid deposits accumulate	Moreno-Gonzalez and Soto (2011)
Familial amyloid polyneuropathy (FAP)	Transthyretin	Peripheral nerves and other tissues	Respiratory and circulatory disorder	Mead and Reilly (2015)

alpha-synuclein in PD, Huntington in HD, and PrP in prion diseases.

Compelling studies have demonstrated that cell dysfunction and death in PMDs are a consequence of the accumulation of misfolded proteins, with intermediate species, some as small as soluble oligomers, representing the most toxic conformation (Caughey and Lansbury 2003; Glabe 2006; Walsh and Selkoe 2007). It has been described that changes in membrane permeability, intracellular calcium levels, mitochondria dysfunction, endoplasmic reticulum stress, and autophagy impairment, among others, could be the mechanisms by which misfolded proteins produce toxicity and cell death (Soto 2003).

Alzheimer's Disease

Alzheimer's disease is one of the most prevalent diseases that affect the elderly (Association 2019). Characterized by irreversible neurodegeneration, it accounts for up to 75% of dementia cases, although "mixed" pathology with vascular disease is common. AD can be due to genetic (also known as familial AD), or sporadic factors, which is the influence of many environmental factors and mutations. The clinical manifestation of familial AD starts at around 30–50 years of age, much earlier than sporadic cases, which peak at 85 years of age (Bateman et al. 2011). Sporadic AD accounts for ~ 70% of the total cases.

Some estimate that every 65 seconds, a person develops Alzheimer's and one of every 2–3 people over 85 years of age will be diagnosed with Alzheimer's. 5.7 million people are currently living with Alzheimer's in 2018, and it has been projected to increase to 13.8 million by 2050 (Association 2019). Also, it has been projected that the annual cost for health care for people with Alzheimer's and other dementias will increase from $277 billion in 2018 to $1.1 trillion in 2050 (Sweeney et al. 2019). Alzheimer's pathology is characterized by the deposition of amyloid plaques, and neurofibrillary tangles (NFTs) that produce cognitive impairment and memory loss (Ballard et al. 2011).

Amyloid plaques are extracellular depositions of misfolded amyloid-β (Aβ) protein in the iso-cortex and subcortical structures, that can be 40 (Aβ-40) or 42 (Aβ-42) amino acids in length, depending on the cleavage of amyloid precursor protein (APP) by presenilin-1 (PSEN1) and presenilin-2 (PSEN2) (Hardy 2006). Alzheimer's pathology is characterized by the overexpression of APP, leading to overproduction of Aβ-40 or Aβ-42 isoforms, which will induce protein misfolding and formation of amyloid plaques (Miya Shaik et al. 2018). It has been demonstrated that genetic variation in APP promoter increases transcription of APP by two to threefold, increasing the risk to develop AD (Liu et al. 2014a). Another example that supports the critical role of APP overexpression in amyloid pathology is in Down syndrome (DS) patients. Nearly all individuals with DS develop typical AD neuropathology (Davidson et al. 2018). Triplication of chromosome 21, where gene coding APP is located, leads to APP overexpression (Wiseman et al. 2015) and development of AD pathology much earlier than in regular individuals (Lemere et al. 1996). The same effect has been observed in Tau neurofibrillary tangles (Adams et al. 2009).

Neurofibrillary tangles are an intracellular accumulation of hyperphosphorylated Tau protein (Ballatore et al. 2007). Tau pathology starts in entorhinal cortex and hippocampus and propagates throughout the iso-cortex (Serrano-Pozo et al. 2011). Neuronal death and loss of synapses in the brain of AD patients are closely correlated with the formation and spreading of hyperphosphorylated Tau and with the clinical features and severity of AD (Serrano-Pozo et al. 2011).

Clinical features of AD mainly involve memory loss, and initially, mild cognitive impairment (MCI) (Borroni et al. 2006). Based on cognitive and functional impairment, the progression of AD pathology can be divided into four stages. Stage 1, or pre-dementia, is characterized by thoughtlessness, and problems with abstract judgement/semantic memory. Stage 2, or early AD, is marked by problems in language, executive functions, and execution of fine movements. In Stage 3 or moderate AD, the clinical progression of the disease is rapid with clear speech difficulties, and the patient becomes dependent on others for many routine activities of daily living. Finally, in stage 4 or advanced AD, patients become severely impaired and dependent on caregivers and family members for all daily and routine activities (Backman et al. 2004; Forstl and Kurz 1999).

Currently, Alzheimer's disease can be only and definitively diagnosed postmortem (Jack et al. 2018). However, a probable diagnosis of AD is possible. To assess whether individuals have cognitive impairment and dysfunction in daily or occupational activities, characteristic of Alzheimer's, the patient and family members give a detailed patient history, which is assessed by a medical provider (Knudsen et al. 2001). Patients are divided into possible or probable AD–dementia.

In 2011, The National Institute on Aging and Alzheimer's Association (NIA-AA) developed new guidelines for the diagnosis of symptomatic or clinical stages of AD, MCI, and AD-related dementia (McKhann et al. 2011; Albert et al. 2011). In addition, a classification of patients without AD symptoms but of preclinical AD was created (Sperling et al. 2011).

A clear definition for symptomatic stages of AD was updated to help in diagnostic decision making and enrollment in clinical trials. Preclinical AD stages were also defined to provide researchers with a common language, where patients were not presenting with symptoms of AD (no cognitive impairment), but with altered AD biomarkers (Sperling et al. 2011; Jack et al. 2011). Commonly used biomarkers for AD include cortical Aβ plaques using positron emission tomography (PET) ligand binding (Ikonomovic et al. 2008; Fleisher et al. 2011) and low levels of Aβ-42 in the cerebrospinal fluid (CSF) (Blennow et al. 2015). Biomarkers for Tau fibrillary tangles are cortical Tau tangles on PET (Villemagne et al. 2015; Brier et al. 2016; Chien et al. 2013), and high levels of hyperphosphorylated Tau protein in the CSF (Buerger et al. 2006). Biomarkers are also used to detect neurodegeneration or neuronal atrophy and include high levels of Tau in the CSF (Toledo et al. 2014; Knopman et al. 2013), fluorodeoxyglucose (FDG)-PET hypometabolism (Wirth et al. 2013), and atrophy on magnetic resonance imaging (MRI) (Prestia et al. 2013).

The utilization of imaging and cerebrospinal fluid (CSF) biomarkers has become fundamental in the diagnosis of AD pathology. It has been estimated that 10–30% of individuals diagnosed clinically with AD (by an expert in AD-related dementia), with normal levels of Aβ-42 in CSF and normal amyloid PET studies (Rowe et al. 2010, 2007; Jack et al. 2008; Zwan et al. 2017), do not have AD neuropathological changes in the brain on postmortem analysis (Nelson et al. 2011). In others, AD neuropathological changes occur without clinical symptoms. It has been demonstrated that 30–40% of cognitive unimpaired (CU) elderly individuals have AD neuropathological changes on autopsy (Johnson et al. 2013; Rodrigue et al. 2012; Rabinovici et al. 2008; Bennett et al. 2006; Price et al. 1991), and a relatively similar percentage of cognitive unimpaired individuals present with abnormal biomarkers (Mormino et al. 2014; Rowe et al. 2010; Jack et al. 2008; Mintun et al. 2006; van Harten et al. 2013b). For this reason, biomarkers have been used to support the diagnosis of AD only in symptomatic individuals.

Alzheimer's disease biomarkers although good indicators of neuropathological changes are independent of AD clinical signs. However, several studies have shown that CU individuals with abnormal amyloid biomarkers have a more rapid progression of atrophy, hypometabolism, and appearance of cognitive decline, compared with individuals with normal amyloid markers (Villemagne et al. 2013; van Harten et al. 2013a; Visser et al. 2009; Rowe et al. 2013). A similar effect has been observed using amyloid PET scans (Rowe et al. 2010).

Several studies have demonstrated that Aβ amyloid pathology is the first abnormality in AD patients with genetic mutations (Cosin-Tomas et al. 2017). Although amyloid deposition alone is not able to produce full AD pathology, it may contribute to downstream pathological changes characteristic of Alzheimer's disease (Chabrier et al. 2012). For this reason, amyloid biomarkers are recognized as the earliest evidence of Alzheimer's pathology in the brain (Bateman et al. 2012; Fleisher et al. 2015; Donohue et al. 2014; Young et al. 2014). However, the presence of Aβ and hyperphosphorylated Tau should be present to diagnose this disease (Table 2).

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA), specifically of the Aβ type, is a vascular centered neurological disease that is characterized by the deposition of aggregated β-amyloid protein

Table 2 Condensed diagnostic criteria table for Alzheimer's disease including variable diagnostic confidence levels based on the presence of Amyloid-β, Tau and neurodegeneration (Knopman et al. 2018; Sarazin et al. 2012; Jack et al. 2018)

Label	Amyloid-β		TAU		Neurodegeneration		
	PET	CSF	PET	CSF	PET	TAU	FDG-MRI
Cognitive unimpaired	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Pathological Alzheimer's change	Abnormal	Low levels	Normal	Normal	Normal	Normal	Normal
Alzheimer's diseases	Abnormal	Low levels	Abnormal	Abnormal	Normal	Normal	Normal
	Abnormal	Low levels	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Alzheimer's or suspected non-Alzheimer's	Abnormal	Low levels	Normal	Normal	Abnormal	Abnormal	Abnormal
Pathological non-Alzheimer's changes	Normal	Normal	Normal	Normal	Abnormal	Abnormal	Abnormal
	Normal	Normal	Abnormal	Abnormal	Normal	Normal	Normal
	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal

in the media and adventitia of small and mid-sized arteries of the cerebral cortex and the leptomeninges (Charidimou et al. 2017). CAA typically leads to cognitive impairment, white matter damage, cortical subarachnoid cerebral microbleeds (CMBs) and often involves spontaneous cortical or subcortical intracerebral hemorrhages referred to as "lobar hemorrhages". Recent studies have suggested as many as 74% of lobar hemorrhages can be ascribed to CAA pathology (Knudsen et al. 2001). As patients age, the prevalence of CAA increases from around 2.3% in 65–74-year-old individuals to as high as 12.1% of patients who are over 85 years of age (Biffi and Greenberg 2011).

Much like AD, two forms of CAA exist: hereditary/familial and sporadic CAA. As a requirement of CAA diagnosis, both sporadic and hereditary CAA must have the characteristic amyloid aggregation in the vasculature. However, the distinction between these comes in the way that they present pathologically and the origin of Aβ misfolding. In hereditary CAA, much like AD, the source of misfolded Aβ can be traced to several genetic mutations among which are those coding for APP, PS1 or PS2. Hereditary CAA has been shown to be almost always comorbid with parenchymal amyloid plaques as well as vascular plaques. Sporadic CAA, however, may be found with parenchymal plaques, but unlike hereditary CAA, the sporadic form can present with vascular pathology alone (Revesz et al. 2002). When comorbid, the cause (hereditary, spontaneous or AD related) of the CAA becomes difficult to distinguish (Fig. 1). As previously mentioned, CAA is often found in patients with AD, yet a growing number of studies have revealed that there are a significant number of patients that present with CAA that do not have AD. While current estimates of general CAA prevalence range from 10–50%, the rate of CAA increases to 80% in AD (Auriel and Greenberg 2012). A key distinguishing factor between CAA and AD is the isoform of Aβ that predominates in the disease. Specifically, the longer Aβ-42 protein is typically found in the plaques associated with AD, while Aβ-40 (two amino acids shorter) is the dominant form of the misfolded protein found in CAA (Zipfel et al. 2009). Some studies have found that the balance between Aβ 40/42 in the brain tends to determine the location of Aβ aggregation (parenchymal or vascular) in AD and CAA (Auriel and Greenberg 2012). However, the precise mechanism leading to CAA is not well understood. It remains unclear whether the Aβ proteins aggregating in CAA are neuronal, vascular or derived from the systemic circulation. The process by which Aβ-40 misfolds is thought to be consistent with the misfolding mechanism of the AD isoform, Aβ-42, which implies a potential for therapeutic overlap between CAA and AD. Current research focuses on the role of the brain's clearance systems and its impairment that allows for Aβ accumulation.

The accumulation of Aβ around vessels is thought to significantly weaken the integrity of the microvasculature of the brain (Fig. 2). This loss of vascular integrity is ultimately the source of the characteristic subarachnoid CMBs and lobar hemorrhages, characteristic of the later stages of the disease. Intracerebral hemorrhage (ICH), while less common, is typically more devastating than ischemic stroke and carries high mortality (Auriel and Greenberg 2012). It has been shown that CAA can also develop after an ischemic injury in which the vasculature is also compromised (Howe et al. 2018a). There are several potential targets that affect the accumulation of Aβ and hemorrhages that present potential therapeutic options, but are involved in complex pathways, therefore making the results contradictory. MMP-9, for example, is a protease that has been shown to be involved in the degradation of the basement proteins, increasing the likelihood of hemorrhage, yet has also been implicated in the degradation of the amyloid fibrils found in plaques associated with AD (Zipfel et al. 2009).

Previously, one of the biggest hurdles associated with CAA management was the difficulty of diagnosing CAA. The diagnostic criteria for CAA required vascular Aβ histological analysis postmortem. In fact, invasive procedures such as brain biopsy were the only diagnostic tools. In recent

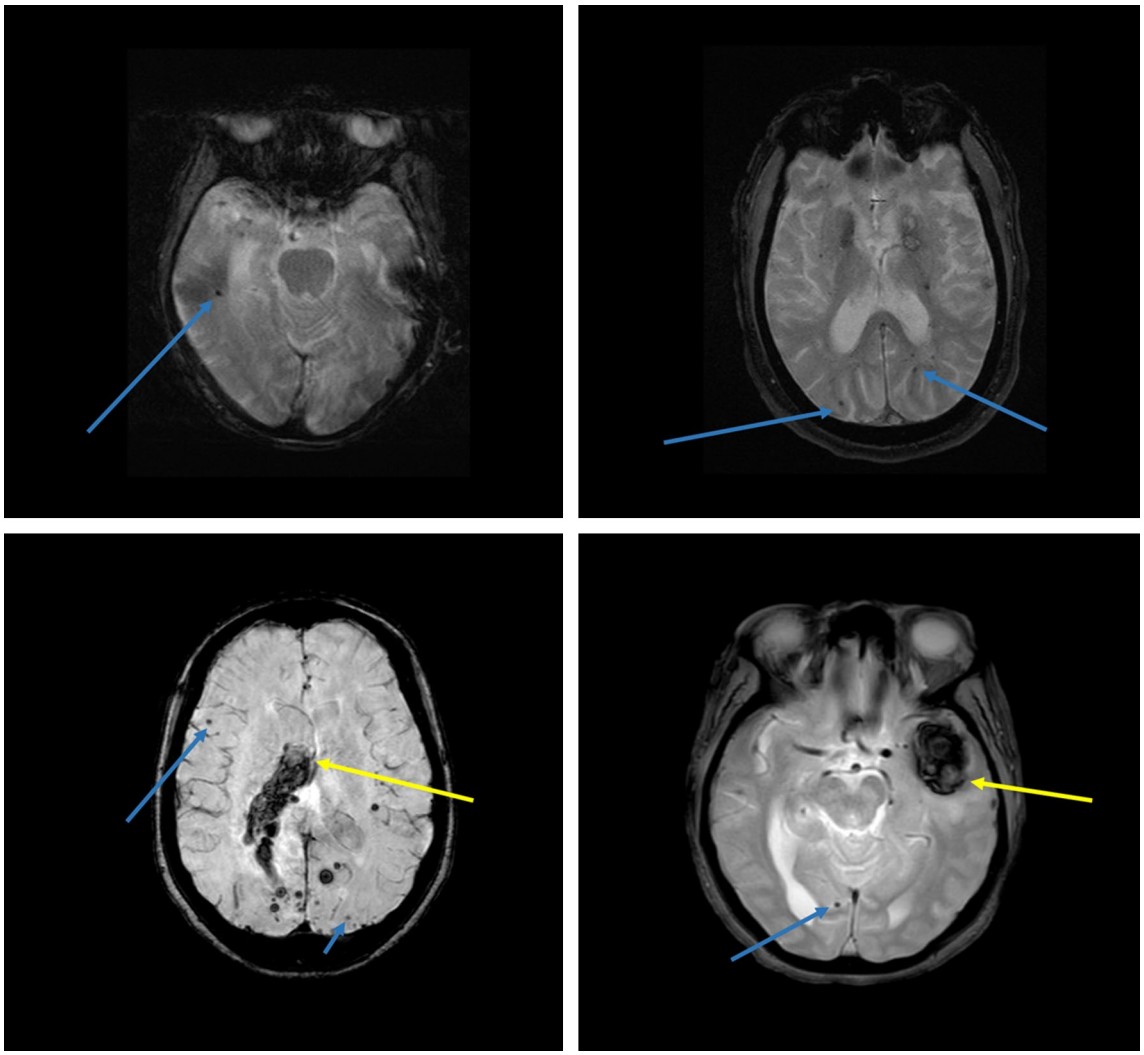

Fig. 1 Top: MRI with GRE (gradient echo) sequence; bottom: SWI (susceptibility-weighted imaging); CAA patients with: blue arrows—cerebral microbleeds (CMBs), yellow arrows—CAA-related intracerebral hemorrhage

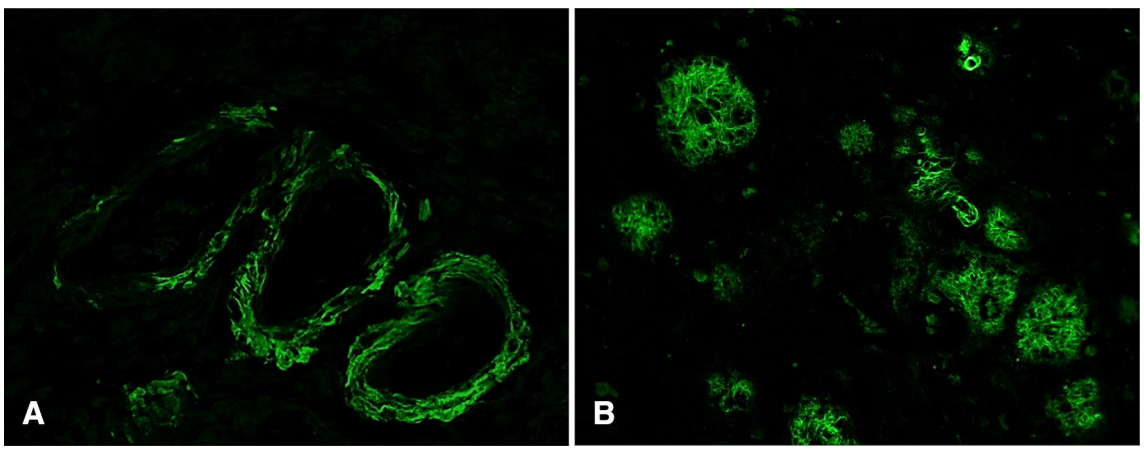

Fig. 2 Thioflavin staining of a CAA patient showing **a** vascular aggregation and **b** parenchymal aggregation of Aβ

years, advances in neuroimaging, most notably MRI, have made it possible to identify CMBs in vivo, but improvements in diagnostic strategies are still needed. To diagnose CAA in patients, a combination of imaging, clinical presentation, and pathological data, the "Boston Criteria" are used (Table 3). There have been several other studies that have tried to identify more convenient and specific methods for CAA diagnosis. Some of these include MMP isoform concentrations, cytokine levels and APOE genes, which can be potential biomarkers/risk factors for CAA. While studies have suggested additional diagnostic criteria, there are many alternative avenues of detection that need to be investigated (Howe et al. 2018b).

Animal Models of CAA and AD

Transgenic animal models for AD and CAA have been developed by utilizing genetic mutations observed in familial cases of AD (FAD) and CAA. The genetic manipulations used to promote amyloid pathology are primarily those involved with the production of APP, Tau or PS1 (Elder et al. 2010). As mentioned previously, both CAA and AD have both a genetic and a sporadic form whose pathologies may differ from one another in important ways (Revesz et al. 2002).

Most of the animal models primarily present with parenchymal amyloid deposition. However, there are two particular models (APP23 and SwDI) that have prominent vascular amyloid deposition with less deposition of amyloid plaques in the parenchyma. Unfortunately, these two models, in addition to a typical FAD pathology, will often develop a vascular pathology as a result of late stages of the disease, therein, blurring the lines between an "AD" mouse model and a "CAA" model. Likewise, the genetic manipulations of CAA models are closely related to those of AD models.

In the past, animal models for CAA were difficult to translate because of insufficient visualization of the CMBs. As these CMBs are the hallmark of CAA, visualizing these in the animal models is vital. Recent studies in our laboratory (unpublished data) have demonstrated the CMBs in SwDI female mice on MRI brain, recapitulating human CAA pathology (Fig. 3). Other groups are developing new models, such as the rat rTgDI so that our understanding of the subtle differences between CAA and AD might be expanded (Davis et al. 2018) (Table 4).

Therapeutic approaches in animal models have focused on controlling the expression of APP (Hebert et al. 2009; Kumar et al. 2019; Li and Wang 2018), modulation of secretases responsible for Aβ-40, and Aβ-42 production (Liu et al. 2014a; Zhu et al. 2012), clearance of Aβ-40 and Aβ-42 proteins (Du et al. 2017; Zhang et al. 2016a), imbalance

Table 3 Criteria created by the Boston Cerebral Amyloid Angiopathy Group: Steven M. Greenberg, MD, Ph.D., Daniel S. Kanter, MD, Carlos S. Kase, MD, and Michael S. Pessin, MD (Greenberg and Charidimou 2018)

Definite CAA	Probable CAA w/pathology	Probably CAA	Possible CAA
Postmortem examination	Clinical data and pathological tissue	Clinical data and radiologic imaging	Clinical data and radiologic imaging
Lobar, cortical corticosubcortical hemorrhage	Lobar, cortical corticosubcortical hemorrhage	Multiple lobar, cortical or cortico-subcortical Hemorrhages	Single lobar, cortical or cortico-subcortical Hemorrhages
Severe CAA vascular Aβ	Some degree of CAA in specimen	Age ≥ 55	Age ≥ 55
Absence of other diagnostic lesion	Absence of other diagnostic lesion	Absence of other cause of hemorrhage	Absence of other cause of hemorrhage

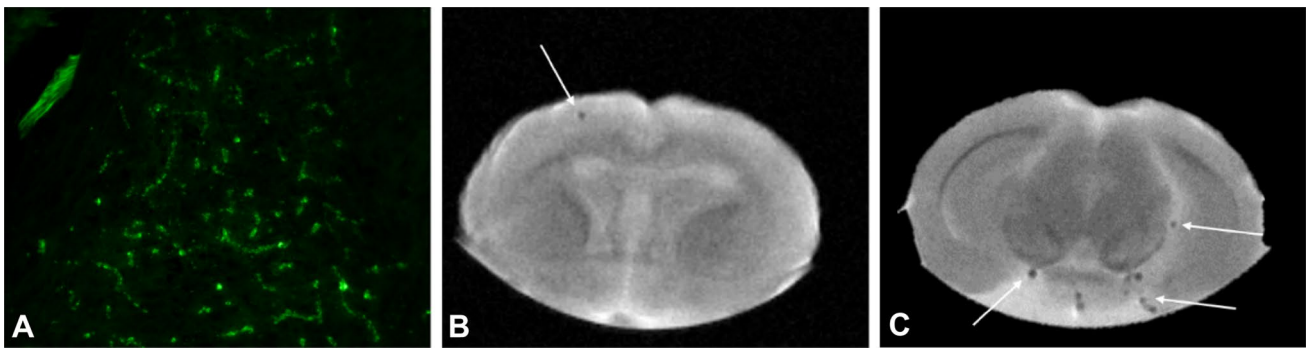

Fig. 3 **a** Thioflavin stain of vascular amyloid-β plaques in TgSwDI mice; T2 star sequence magnetic resonance imaging of **b** cortical, **c** hippocampal, thalamic and midbrain CMBs in TgSwDI mice

Table 4 A collection of various mouse models of Aβ related disease including the gene mutation, mutated promoter, and a description of phenotype

Animal models of Aβ related disorders					
Line	Gene	Mutation	Promotor	Pathology	References
Tg2576	APP	APP (isoform 695) with double mutation K670 N, M671L (Swedish mutation)	Prion	Parenchymal with some vascular	Hsiao et al. (1996)
APP23	APP	APP (isoform 751) with Swedish (KM670/671NL) mutation	Thy1	Parenchymal plaques	Sturchler-Pierrat et al. (1997)
APPDutch	APP	APP (isoform 751) with E693Q mutation	Thy1	Vascular deposition of amyloid with few parenchymal plaques	Herzig et al. (2004)
3×Tg	APP, PSEN1, MAPT	APP with the Swedish mutation, PSEN1 with the PS1M146 V, and MAPT with the P30IL mutation	Thy1.2	Parenchymal plaques combined with tau pathology	Chase (1992)
5xFAD (C57BL6)	APP, PSEN1	APP Swedish, Florida, and London mutations, and PSEN1 including the M146L and L286 V mutations	Thy1	Parenchymal plaques	Jawhar et al. (2012) and Richard et al. (2015)
APP E693Δ-Tg (Osaka)	APP	APP (isoform 695) with the Osaka mutation	Prion	Parenchymal plaques	Tomiyama et al. (2010)
APP Knock-out	APP	Inactivation of the mouse APP gene		No plaques	Zheng et al. (1995)
APPSwe	APP	APP (isoform 751) with the Swedish mutation	Thy1.2	Parenchymal plaques	Richards et al. (2003)
APPswe/PSEN1dE9	APP, PSEN1	APP gene (isoform 695) Swedish mutation and v mice express a mutant human PSEN1 gene carrying the deletion of exon 9 (dE9)	Prion	Parenchymal plaques	Jankowsky et al. (2001, 2004)

Additional information on AD Tg models can be found at the Web site of the Alzheimer's Association (http://www.alzforum.org/res/com/tra)

between hyperphosphorylation (kinases) (Liu et al. 2016) and de-phosphorylation (phosphatases) (Liu et al. 2016) processes of TAU (Sierksma et al. 2018; Jiang et al. 2018), and inhibition of neurotoxicity (Zhao et al. 2018; Higaki et al. 2018; Zhang et al. 2015) and synaptic loss (Xu et al. 2019; Hu et al. 2015) pathways.

MicroRNAs, a class of non-coding RNAs, are well-known regulators for post-translational gene expression of different proteins and critical in many fundamental biological events such as neurodegenerative processes (Huang et al. 2011; Hammond 2015). A very important characteristic of microRNAs is that one microRNA can targets numerous protein genes, and one gene could be regulated by multiple microRNAs. These make microRNAs a potential tool to investigate multifactorial diseases, such as AD and CAA (Iqbal and Grundke-Iqbal 2010; Wolfe 2014).

MicroRNA and Their Involvement in AD and CAA

miRNA

MicroRNAs are complex molecules that have a wide variety of effects. Generally, our concept of protein creation is that DNA is transcribed, processed into mRNA and then the mRNA is translated into protein. However, only a fraction of the nucleotides that make up the human genome are actually used to code for proteins. In recent years, many of these unidentified nucleotide sequences have been identified as other variations of RNA molecules. Many of these do not code for proteins but regulate the translation of mRNA into protein. One form of non-coding

RNA, microRNA (miRNA), has a primary role in regulating the translational activity of a cell. Within the genome, sequences coding for miRNA can be found in intergenic regions (52%), introns (40%) and exons (8%) (Hsu et al. 2006).

miRNAs are transcribed in the same way as other RNA molecules, but the specific sequences of miRNAs cause their structure and function to be different from mRNA. The specific sequences of the unprocessed pre-miRNA form a characteristic hairpin loop after complementary sequences produce auto-binding. After being exported into the cell cytoplasm, these pre-miRNA molecules are cleaved by a Dicer/TRBP complex that cuts the miRNA so that all that remains is a double-stranded short miRNA molecule (Mohr and Mott 2015). Once processed and cleaved, the miRNA is further processed by a complex of Argonaute family protein that separates the two stands and anneals the sequence of the miRNA strand to the complementary sequence of the target mRNA segment. Once bound to its target, the miRNA can affect the protein synthesis process in several ways that result in increased or decreased production of the target protein (Terrinoni et al. 2018) (Fig. 4).

miRNA molecules are analogous to the throttle of target protein translation. Their activity has been shown to result in both increase and decrease in the levels of different proteins, but the level of effect ranges due to specific cellular pathways and complementarity to the target strand. It is currently believed that miRNAs control the production of about 30% of the known genes in protein synthesis (Filipowicz et al. 2008).

When miRNAs bind to their target mRNA sequences, the level of complementarity determines much of the mechanism and the method of regulation these molecules perform. When miRNA bind to mRNA molecules, often the miRNA molecules bind with incomplete complementarity and they repress the translation of mRNA sequences, as opposed to completely blocking their translation. When complementarity is perfect, the mRNA molecule cannot be translated, ultimately leading to mRNA degradation. However, if the miRNA is not perfectly bound to mRNAs, then three primary mechanisms repress the translation of the mRNA. One option is similar to the outcome of perfect complementarity in that the miRNA prevents the translation of the mRNA while recruiting deadenylases to degrade the mRNA poly-A tail, leading to a decrease in translation. Second, miRISC complexes can block the 5′ end of an mRNA from binding to the ribosomes necessary to translate the sequence, thus preventing the initiation of the translational process. Lastly, miRISC complexes can alter the structural nature of mRNA strands which can "knock off" the ribosomes after initiation and prevent the elongation of mRNA translation (Terrinoni et al. 2018).

miRNA transcripts are abundant within our body and control many cellular processes. miRNA and their role in diseases have been increasingly recognized. In various diseases, the processes that are faulty or overactive are often controlled, albeit indirectly, by these miRNAs. Individual miRNA can be both tissue specific, as well as functionally specific in multiple tissues. However, the most significant advantage of using miRNA as a potential diagnostic or therapeutic tool is the ability to measure circulating miRNA (c-miRNA). Circulating miRNAs are preferentially released when a cell is under stress such as during injury, inflammation, necrosis or apoptosis (Terrinoni et al. 2018). In fact, in much the same way, certain miRNA molecules appear tissue specific, some have shown that certain pathological conditions have an associated cellular release of specific c-miRNA that could potentially serve as biomarkers for disease (Chen et al. 2008).

MicroRNA, Diagnostics, and Therapy

Due to the relatively small size of miRNA, they have the ability to pass nearly seamlessly between cells, out of cells and into the peripheral circulatory system. When miRNAs (as well as many pre-miRNA and pri-miRNA) enter the circulatory system, they do so via exosomes or insulated by RNA-binding proteins (Simpson et al. 2009). Unlike free-floating mRNAs, which are quickly degraded by RNases, these miRNAs are transported throughout the body with "insulation" allowing their half-life to be significantly longer (5 days or more, in some cases) (Gantier et al. 2011). This extended half-life along with the relatively high mobility of these molecules means they can be exploited for diagnosis of disease conditions.

miRNAs, notably circulating miRNA (c-miRNA) molecules, are found in many bodily fluids including blood, urine, saliva, breast milk and CSF (Terrinoni et al. 2018). This suggests that miRNA level assessment in pathological conditions is cheap and relatively convenient. The stability of these molecules also allows the time between sample collection and analysis to be much longer.

Problematic Analysis/Difficulty of Specificity

miRNAs, while easy to obtain and process, pose several analytical hurdles to their use as diagnostic or therapeutic tools. Understanding the wide expanse of miRNA in the body can be complex for several reasons. For one, over 2500 different miRNA molecules have been identified, and there are likely many more. In addition, others have found examples of single miRNA molecules involved in multiple forms of cancer, but are upregulated in some and down-regulated in others (Banzhaf-Strathmann and Edbauer 2014;

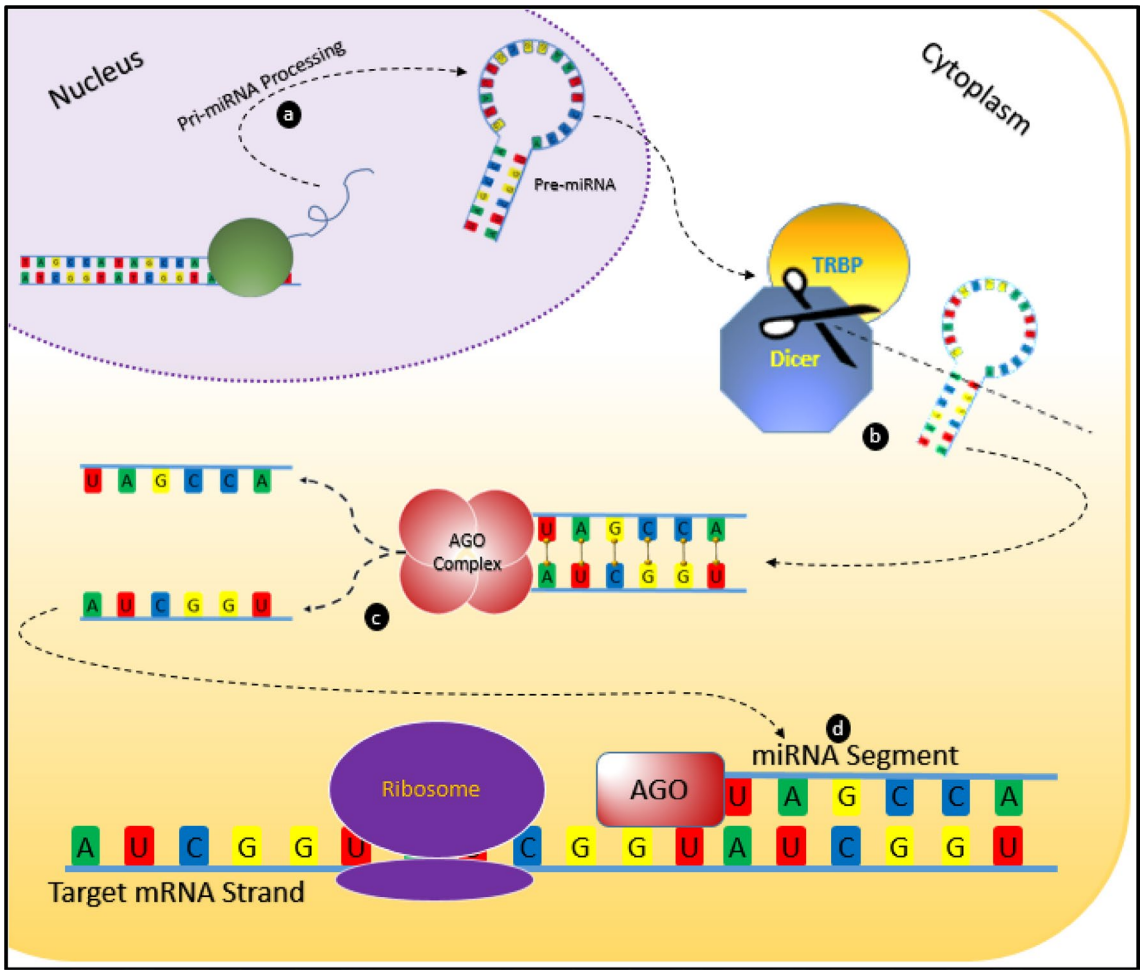

Fig. 4 *a* A miRNA sequence is transcribed as pri-miRNA and processed into pre-miRNA. *b* Dicer and TRBP cleave pre-miRNA to form double-stranded miRNA. *c* Argonaute protein complex (AGO) separates miRNA into two single-stranded segments. *d* miRNA segment binds to target mRNA strand, with help from AGO, preventing the translation of the protein

Helwak et al. 2013). It is difficult to tie the individual effects of miRNA to specific outcomes. Likewise, due to the ability of miRNA to regulate a target molecule with imperfect binding to the transcript, identification of all the possible targets of each miRNA is a daunting task (Mohr and Mott 2015; Simonson and Das 2015). In effect, the wide-ranging effects of miRNA, the sheer number of them, and the difficulty of identifying the targets of these miRNAs with specificity make miRNAs, as useful and informative as they are, a difficult source of scientific answers.

Theoretical Therapies

Current research on the use of miRNA pathways as targets of therapy aims to inhibit the effects of miRNA that are presumed to be dysregulated in a healthy cell. There are three potential approaches to inhibit the regulatory effects of miRNA as therapies that have been studied: expression vectors (sometimes referred to as miRNA sponges), anti-miRNA oligonucleotides, and small molecule inhibitors.

Expression vectors are mutated or synthetic segments of RNA that are mutated so they are unable to be translated, but still have the complementary sequence that attracts and binds to miRNA, in turn, preventing them from affecting their target mRNA. If there was a miRNA that played a significant role in the process of a disease, then expression vectors provide a way to "distract" miRNA and intervene in the target cellular process (Hebert et al. 2010; Simonson and Das 2015). In effect, expression vectors prevent the binding of miRNAs by obstructing target mRNA-binding sites.

Anti-miRNA oligonucleotides (AMOs) are another form of miRNA control that may be valuable as a therapeutic target. AMOs are designed segments of nucleotides that match the sequences of the miRNA they are targeting to suppress. In this mechanism, the AMO segments are complementary to the sequences of miRNA, and binding of AMOs to

miRNA can have one of two effects. First, the AMO binding to the miRNA can block the sequence of miRNA that would ordinarily bind to the target mRNA, and thus AMO binding to miRNA will inhibit the ability of the miRNA to regulate mRNA. Alternatively, the binding of AMOs to miRNA can lead to the recruitment of RNases that degrade the miRNA before they are able to affect its target. Therefore, the complementary sequence of miRNA that matches target mRNA molecules is already blocked, preventing them from ever binding and affecting the mRNA molecule (Lennox and Behlke 2010). In contrast to expression vectors, AMOs prevent binding of miRNAs by obstructing miRNA-binding sites.

While effective and specific, expression vectors and AMOs are difficult and expensive to produce and administer. Small molecule inhibitors of miRNA (SMIR), on the other hand, represent a large group of potential molecules that play a role of miRNA in translational regulation. Many types of molecules can be considered SMIRs, but generally, they have some effect on the transcription of miRNAs. This can be the processing of pre-miRNA or the interactions between mRNAs, miRNAs and the protein complexes that bind them. In many cases, these small molecules have already been FDA approved and thus present a more expedient implementation process. However, these molecules have been shown to be less specific than other therapeutic approaches as they tend to act on general miRNA pathways rather than on individual miRNA sequences (Shan et al. 2008).

While a majority of research has been dedicated to finding methods of inhibiting miRNA, many miRNAs are beneficial or are downregulated in pathological conditions. Recently, the focus has been directed at replacing the miRNA that is downregulated, to prevent or delay the effects of the disease. In many diseases, such as cancer and neurodegenerative disease, the pathological phenotype is caused by a lack of inhibition that may be a result of the loss of regulatory miRNAs (Simonson and Das 2015). While replacement miRNA therapy is not well established, the theoretical ability to regain control over dysregulated pathological conditions is a highly promising area. However, the delivery of miRNA to an animal or patient remains challenging and methods to do so, while currently being attempted, have yet to be well established (Simonson and Das 2015).

MicroRNA and Neurodegenerative Diseases

miRNAs play an important role in the brain (Ameres and Zamore 2013; Barry 2014; Bartel 2009; Londin et al. 2015). One of the first experiments performed to show the importance of miRNA in the brain used a mutated version of Dicer in zebrafish, which resulted in defects in brain structure and morphogenesis. However, when the normal miRNA was reintroduced, the phenotype was rescued (Giraldez et al. 2005).

The brain is a large source of miRNA, and it has been shown that miRNAs in the brain display a very particular expression pattern, which is fundamental for the regulation of important biological processes such as, neuronal plasticity, metabolism, neurogenesis, cell proliferation, apoptosis, and neuronal differentiation (Goodall et al. 2013; Nelson et al. 2003; Kosik and Krichevsky 2005). Also, it is important to highlight that a single miRNA has been correlated with hundreds of different mRNAs, making them an important player in central nervous system (CNS) development (Lewis et al. 2005).

Several studies have shown dysregulation of miRNA expression patterns in the brain in several neurodegenerative diseases (Nelson and Keller 2007; Lukiw 2007; Lim et al. 2005). A correlation between different stages of neurodegenerative diseases and specific patterns of miRNA expression has become a powerful tool for diagnosis and treatment.

MicroRNA in Alzheimer's Disease and CAA

A critical challenge has been to identify molecular markers to diagnose AD at preclinical or early stages. Patients with AD-related mild cognitive impairment have the neuropathological characteristic of dementia–AD (Morris et al. 2001; Morris and Cummings 2005), and it has been demonstrated that 50% of MCI patients progress to AD-related dementia (ADRD) (Martinez and Peplow 2019).

ADRD progression includes the progressive loss of neurons, decreases in synapses, and reduction in volume and weight of the hippocampus. Studies have found a strong correlation between the loss of neurons and synapses with impairments in cognition and memory in AD patients (Reddy et al. 2012). Several groups have demonstrated changes in miRNA expression in MCI patients compared to normal control individuals (Kumar et al. 2017; Kayano

et al. 2016). Studies have found dysregulation of miRNAs in AD, specifically in key genes related to AD pathology such as APP (Patel et al. 2008) and β-secretase 1 (BACE1) (Yang et al. 2003), which regulate the production of Aβ. Deficits in the clearance of Aβ peptide may be another important contributor to the formation of Aβ plaques in the brain (Millan 2017). (Hardy and Selkoe 2002). Several studies have shown that miRNAs are involved in Aβ clearance (Tiribuzi et al. 2014; Toyama et al. 2017). Specifically, it has been shown that miRNAs are able to control autophagic–lysosomal degradation of Aβ, one of the major mechanisms to eliminate Aβ (Nixon 2013; Rubinsztein et al. 2012; Bohm et al. 2015). Another important contributor to AD pathology is the direct neurotoxicity of Aβ. Several studies have shown that Aβ neurotoxicity can be reversed by miRNA (Li et al. 2016; He et al. 2017). Lastly, miRNAs have been closely related to the synaptic dysfunction induced by abnormal Aβ metabolism (Hu et al. 2015). Studies have shown that synaptic dysfunction and cognitive impairment caused by Aβ can be restored by manipulation of miRNAs, providing solid evidence that dysregulation in miRNA expression are critical in the synaptic dysfunction and cognitive impairment observed in AD patients.

Tau protein can be found in phosphorylated or dephosphorylated forms, which allows Tau to be either associated or not with microtubules. This process is closely regulated by a large number of kinase or phosphatase enzymes (Ballatore et al. 2007; Absalon et al. 2013). Studies have shown that miRNAs regulate these kinases and phosphatases, which could lead to the production of hyperphosphorylated tangles (Smith et al. 2015; Liu et al. 2016). Changes in the pattern of miRNA expression have been associated with Tau hyperphosphorylation in the brains of AD patients (Smith et al. 2015; Singer et al. 2005). Several groups have observed the altered pattern of miRNAs expression not only in the brain, but in the blood, and CSF as well (Sierksma et al. 2018; Hebert et al. 2010; Cogswell et al. 2008) (Tables 5 and 6).

Investigation of the role of miRNAs in CAA is limited. Only two miRNAs have been identified that have a specific association with CAA. Nicolas et al. examined the DNA sequence of patients with probable CAA. They focused on the APP 3'UTR and identified a mutated gene sequence that was associated with the development of CAA, even in patients without a family history. After analysis, they identified two miRNA molecules that matched the sequence of the CAA associated gene mutation, miR-582-3p and miR-892b. Their work identified that miR-892b downregulated the production of APP, but that the CAA associated mutation blocked its effects. In addition, they found that the identified mutation allowed miR-582-3p to bind to the sequence and increase the production of APP (Nicolas et al. 2016).

Conclusions

In this review, we have highlighted new research examining the potential role of miRNA in AD and CAA. We compiled the known miRNA literature that may be involved in the pathogenesis or progression of CAA and AD, however, the exact role of miRNA in neurodegenerative diseases remains to be determined. The similarity between CAA and AD, along with the vast amount of emerging research related to miRNA and AD, leads us to believe that previously identified miRNA molecules may represent an accessible avenue for research into possible CAA biomarkers. The value of miRNA, either as biomarkers or as therapeutic targets, will become clearer as we improve our understanding of miRNA regulation and function. Biomarkers for CAA and AD could be extremely valuable, especially early in the disease, when intervention is likely to be most effective. This is especially true in CAA, as a diagnosis before a large lobar hemorrhage could have implications for patient management, such as avoiding anticoagulants in these patients at risk.

Table 5 Human AD miRNA and affected pathway/protein

	MiRNA	Relevant pathway	Tissue	Expression in AD	References
Human	miR-20a	APP	Brain	Down	Wang et al. (2011)
	miR-106b	APP	Brain	Down	Hebert et al. (2009)
			Serum/blood	Up/down	Cheng et al. (2015) and Yilmaz et al. (2016)
			Blood	Up	Cheng et al. (2015)
	miR-153	APP	Brain	Down	Long et al. (2012)
	miR-106a	APP	Brain	Down	Wang et al. (2011)
			Serum/blood	Up/down	Cheng et al. (2015) and Yilmaz et al. (2016)
	miR-101a	App	Brain	Down	Hebert et al. (2008)
			CSF	Down	Burgos et al. (2014)
	miR-124	APP	CSF	Down	Burgos et al. (2014)
	miR-16	APP	CSF	Down	Muller et al. (2016b)
	miR-9	APP	Brain	Down	Hebert et al. 2008)
			Brain	Up	Lukiw (2007)
			CSF	Up/down	Alexandrov et al. (2012) and Burgos et al. (2014)
	miR-20b	APP	Brain	Down	Nunez-Iglesias et al. (2010)
	miR-21	APP	Brain	Down	Wang et al. (2011)
	miR-181c	APP	Serum	Down	Geekiyanage et al. (2012) and Hong et al. (2017)
			CSF	Down	Cogswell et al. (2008)
	miR-30c	APP	Brain	Down	Cogswell et al. (2008)
	miR-148b	APP	Blood	Up	Satoh et al. (2015)
	miR-29c	BACE1	Brain	Down	Lei et al. (2015)
			CSF	Down	Gui et al. (2015)
			Blood	Down	Yang et al. (2015)
	miR-135b	BACE1	Blood	Down	Zhang et al. (2016b) and Zhang et al. (2016)
	miR-195-5p	BACE1	Serum	Up	Wu et al. (2017)
			CSF	Down	Wu et al. (2017)
	miR-107	BACE1	Brain	Down	Wang et al. (2008)
			Plasma/blood	Down	Leidinger et al. (2013) , Wang et al. (2015) and Yilmaz et al. (2016)
	miR-485-3p	BACE1	CSF	Up	Gui et al. (2015)
	miR-29a	BACE1	Brain	Down	Hebert et al. (2008)
			CSF	Up	Muller et al. (2016a)
			Serum	Down	Geekiyanage et al. (2012)
	miR-29b-1	BACE1	Brain	Down	Hebert et al. (2008)
			Serum	Down	Geekiyanage et al. (2012)
			Blood	Down	Satoh et al. (2015)
	miR-146a	Tau	Brain	Up	Lukiw et al. (2008)
			CSF	2 Down/2 up	Kiko et al. (2014), Muller et al. (2014), Denk et al. (2015) and Alexandrov et al. (2012)
			Plasma/serum	Down	Kiko et al. (2014) and Dong et al. (2015)
	miR-15	Tau	Brain	Down	Hebert et al. (2008)
	miR-497	Tau	Serum	Up	Wu et al. (2017)
			CSF	Down	Burgos et al. (2014) and Riancho et al. (2017)
	miR-181c	Tau	Brain	Down	Hebert et al. (2008)

Table 5 (continued)

MiRNA	Relevant pathway	Tissue	Expression in AD	References
miR-132	Tau/Neurotoxicity	CSF	Down	Burgos et al. (2014)
miR-128	Aβ Clearance	Brain	Up	Lukiw (2007)
		CSF	Up	Alexandrov et al. (2012)
miR-34a	Aβ Clearance/synaptic dysfunction	Plasma	Up/down	Bhatnagar et al. (2014), Cosin-Tomas et al. (2017), Kiko et al. (2014) and Schipper et al. (2007)
		CSF	Up/down	Alexandrov et al. (2012) and Kiko et al. (2014)
		Plasma	Up/down	Bhatnagar et al. (2014) and Kiko et al. (2014)
		Serum	Up	Burgos et al. (2014)
miR-124	BACE1/synaptic dysfunction	Brain	Down	Smith et al. (2011)
miR-125b	Synaptic dysfunction	Brain	Up	Cogswell et al. (2008)
		CSF	2 Down/2 up	Galimberti et al. (2014), Alexandrov et al. (2012), Muller et al. (2016a) and Kiko et al. (2014)
		Serum	2 Down/1 up	Galimberti et al. (2014), Tan et al. (2014) and Burgos et al. (2014)
		Plasma		Kiko et al. (2014)
miR-132	Synaptic dysfunction	Brain	Down	Cogswell et al. (2008)
miR-134	Synaptic dysfunction	Brain	Up	Nunez-Iglesias et al. (2010)
miR-138	Synaptic dysfunction	CSF	Up	Siegel et al. (2009)
miR-219	Synaptic dysfunction	CSF	Down	Denk et al. (2015)
		Serum	Up	Burgos et al. (2014)
miR-15a	Neurotoxicity	Plasma	Up	Bekris et al. (2013)
		Blood	Down	Satoh et al. (2015)
miR-34c	Neurotoxicity	Plasma	Up	Bhatnagar et al. (2014)
		Serum	Up	Burgos et al. (2014)
		Plasma/serum	Up	Grasso et al. (2014)

Table 6 Model AD miRNA and affected pathway/protein

	MiRNA	Relevant pathway	Tissue	Expression in AD	References
Mouse	miR-17-5p	APP	Brain	Down	Hebert et al. (2009)
	miR-107	BACE1, Tau	Brain	Down	Wang et al. (2008) and Yao et al.(2010)
	miR-106b	APP/Tau	Brain	Down	Liu et al. (2016) and Hebert et al. (2009)
	miR-153	APP	Brain	Down	Liang et al. (2012)
	miR-16	APP	Embryo	Down	Liu et al. (2012)
	miR-200b	APP	Brain	Down	Liu et al. (2014b)
	miR-195	BACE1	Brain	Down	Zhu et al. (2012)
	miR-135a	BACE1	Brain	Down	Liu et al. (2014b)
	miR-135b	BACE1	Brain	–	Zhang et al. (2016b)
	miR-146a	Tau	Brain/CSF	Up	Wang et al. (2016)
	miR-132	APP/Tau	Brain	Down	Salta et al. (2016), Hernandez-Rapp et al. (2016) and Smith et al. (2015)
	miR-212	Tau	Brain	Down	Hernandez-Rapp et al. (2016) and Smith et al. (2015)
	miR-125b	Tau	Brain	Up	Banzhaf-Strathmann et al. (2014)
	miR-103	Tau	Brain	Down	Yao et al. (2010)
	miR-20b	Synaptic dysfunction	Brain	Down	Schratt (2009)
	miR-148	Synaptic dysfunction	Brain	Down	Schratt (2009)
	miR-361	Neuronal apoptosis	Brain	Down	Schonrock et al. (2010)
	miR-409-3p	Neuronal apoptosis	Brain	Down	Schonrock et al. (2010)
	miR-34a	Aβ clearance/synaptic dysfunction	Brain	Up	Schipper et al. (2007) and Xu et al. (2018)
	miR-124	Synaptic dysfunction	Brain	Up	Wang et al. (2018)
	miR-188-5p	Synaptic dysfunction	Brain	Down	Lee et al. (2016)
	miR-330	Neurotoxicity	Brain	Up	Zhou et al. (2018)
	miR-181b	APOE	Brain	PMBC	Schipper et al. (2007)
	miR-29	BACE1	Serum	Down	Shioya et al. (2010) and Geekiyanage et al. (2012)
	miR-9	Tau	Serum	Down	Schonrock and Gotz (2012)
	miR-137	Neurotoxicity	Brain	–	He et al. (2017)
	miR-10a	Neuronal apoptosis	Brain	Up	Wu et al. (2018)
Rat	miR-26b	Tau/neuronal apoptosis	Brain	Up	Absalon et al. (2013)
	miR-34c	Synaptic dysfunction	Plasma, brain	–	Bhatnagar et al. (2014) and Hu et al. (2015)
Rat/Mouse	miR-101	APP/Tau	Brain	Down	Miya Shaik et al. (2018) and Vilardo et al. (2010)

Acknowledgements This work was supported by NIH/NINDS NS094543 and NS096493 (to LDM).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

Absalon, S., Kochanek, D. M., Raghavan, V., & Krichevsky, A. M. (2013). MiR-26b, upregulated in Alzheimer's disease, activates cell cycle entry, tau-phosphorylation, and apoptosis in postmitotic neurons. *Journal of Neuroscience, 33*(37), 14645–14659. https://doi.org/10.1523/JNEUROSCI.1327-13.2013.

Adams, S. J., Crook, R. J., Deture, M., Randle, S. J., Innes, A. E., Yu, X. Z., et al. (2009). Overexpression of wild-type murine tau results in progressive tauopathy and neurodegeneration. *American Journal of Pathology, 175*(4), 1598–1609. https://doi.org/10.2353/ajpath.2009.090462.

Akter, R., Cao, P., Noor, H., Ridgway, Z., Tu, L. H., Wang, H., et al. (2016). Islet amyloid polypeptide: Structure, function, and pathophysiology. *Journal of Diabetes Research, 2016,* 2798269. https://doi.org/10.1155/2016/2798269.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Alexandrov, P. N., Dua, P., Hill, J. M., Bhattacharjee, S., Zhao, Y., & Lukiw, W. J. (2012). microRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extracellular

fluid (ECF). *International Journal of Biochemistry and Molecular Biology, 3*(4), 365–373.
Ameres, S. L., & Zamore, P. D. (2013). Diversifying microRNA sequence and function. *Nature Reviews Molecular Cell Biology, 14*(8), 475–488. https://doi.org/10.1038/nrm3611.
Andersen, P. M., & Al-Chalabi, A. (2011). Clinical genetics of amyotrophic lateral sclerosis: What do we really know? *Nature Reviews Neurology, 7*(11), 603–615. https://doi.org/10.1038/nrneurol.2011.150.
Association, A. s. (2019). Alzheimer's disease facts and figures. *Alzheimers Dement 15(3):*321-387.
Auriel, E., & Greenberg, S. M. (2012). The pathophysiology and clinical presentation of cerebral amyloid angiopathy. *Current Atherosclerosis Reports, 14*(4), 343–350. https://doi.org/10.1007/s11883-012-0254-z.
Backman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2004). Multiple cognitive deficits during the transition to Alzheimer's disease. *Journal of Internal Medicine, 256*(3), 195–204. https://doi.org/10.1111/j.1365-2796.2004.01386.x.
Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019–1031. https://doi.org/10.1016/S0140-6736(10)61349-9.
Ballatore, C., Lee, V. M., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nature Reviews Neuroscience, 8*(9), 663–672. https://doi.org/10.1038/nrn2194.
Banzhaf-Strathmann, J., Benito, E., May, S., Arzberger, T., Tahirovic, S., Kretzschmar, H., et al. (2014). MicroRNA-125b induces tau hyperphosphorylation and cognitive deficits in Alzheimer's disease. *EMBO Journal, 33*(15), 1667–1680. https://doi.org/10.15252/embj.201387576.
Banzhaf-Strathmann, J., & Edbauer, D. (2014). Good guy or bad guy: The opposing roles of microRNA 125b in cancer. *Cell Communication and Signaling, 12,* 30. https://doi.org/10.1186/1478-811X-12-30.
Barry, G. (2014). Integrating the roles of long and small non-coding RNA in brain function and disease. *Molecular Psychiatry, 19*(4), 410–416. https://doi.org/10.1038/mp.2013.196.
Bartel, D. P. (2009). MicroRNAs: Target recognition and regulatory functions. *Cell, 136*(2), 215–233. https://doi.org/10.1016/j.cell.2009.01.002.
Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., et al. (2011). Autosomal-dominant Alzheimer's disease: A review and proposal for the prevention of Alzheimer's disease. *Alzheimers Research & Therapy, 3*(1), 1. https://doi.org/10.1186/alzrt59.
Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., et al. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *New England Journal of Medicine, 367*(9), 795–804. https://doi.org/10.1056/NEJMoa1202753.
Bekris, L. M., Lutz, F., Montine, T. J., Yu, C. E., Tsuang, D., Peskind, E. R., et al. (2013). MicroRNA in Alzheimer's disease: An exploratory study in brain, cerebrospinal fluid and plasma. *Biomarkers, 18*(5), 455–466. https://doi.org/10.3109/1354750X.2013.814073.
Bennett, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., et al. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology, 66*(12), 1837–1844. https://doi.org/10.1212/01.wnl.0000219668.47116.e6.
Bhatnagar, S., Chertkow, H., Schipper, H. M., Yuan, Z., Shetty, V., Jenkins, S., et al. (2014). Increased microRNA-34c abundance in Alzheimer's disease circulating blood plasma. *Frontiers in Molecular Neuroscience, 7,* 2. https://doi.org/10.3389/fnmol.2014.00002.
Biffi, A., & Greenberg, S. M. (2011). Cerebral amyloid angiopathy: A systematic review. *Journal of Clinical Neurology, 7*(1), 1–9. https://doi.org/10.3988/jcn.2011.7.1.1.
Blennow, K., Mattsson, N., Scholl, M., Hansson, O., & Zetterberg, H. (2015). Amyloid biomarkers in Alzheimer's disease. *Trends in Pharmacological Sciences, 36*(5), 297–309. https://doi.org/10.1016/j.tips.2015.03.002.
Bohm, C., Chen, F., Sevalle, J., Qamar, S., Dodd, R., Li, Y., et al. (2015). Current and future implications of basic and translational research on amyloid-beta peptide production and removal pathways. *Molecular and Cellular Neuroscience, 66*(Pt A), 3–11. https://doi.org/10.1016/j.mcn.2015.02.016.
Borroni, B., Di Luca, M., & Padovani, A. (2006). Predicting Alzheimer dementia in mild cognitive impairment patients. Are biomarkers useful? *European Journal of Pharmacology, 545*(1), 73–80. https://doi.org/10.1016/j.ejphar.2006.06.023.
Brier, M. R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., et al. (2016). Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. *Science Translational Medicine, 8*(338), 338ra366. https://doi.org/10.1126/scitranslmed.aaf2362.
Buerger, K., Ewers, M., Pirttila, T., Zinkowski, R., Alafuzoff, I., Teipel, S. J., et al. (2006). CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. *Brain, 129*(Pt 11), 3035–3041. https://doi.org/10.1093/brain/awl269.
Burgos, K., Malenica, I., Metpally, R., Courtright, A., Rakela, B., Beach, T., et al. (2014). 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*(5), e94839. https://doi.org/10.1371/journal.pone.0094839.
Caughey, B., & Lansbury, P. T. (2003). Protofibrils, pores, fibrils, and neurodegeneration: Separating the responsible protein aggregates from the innocent bystanders. *Annual Review of Neuroscience, 26,* 267–298. https://doi.org/10.1146/annurev.neuro.26.010302.081142.
Chabrier, M. A., Blurton-Jones, M., Agazaryan, A. A., Nerhus, J. L., Martinez-Coria, H., & LaFerla, F. M. (2012). Soluble Abeta promotes wild-type tau pathology in vivo. *Journal of Neuroscience, 32*(48), 17345–17350. https://doi.org/10.1523/JNEUROSCI.0172-12.2012.
Charidimou, A., Boulouis, G., Gurol, M. E., Ayata, C., Bacskai, B. J., Frosch, M. P., et al. (2017). Emerging concepts in sporadic cerebral amyloid angiopathy. *Brain, 140*(7), 1829–1850. https://doi.org/10.1093/brain/awx047.
Chase, W. R. (1992). You gave me back my life. *Journal of the Michigan Dental Association, 74*(7), 28–30.
Chen, X., Ba, Y., Ma, L., Cai, X., Yin, Y., Wang, K., et al. (2008). Characterization of microRNAs in serum: A novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Research, 18*(10), 997–1006. https://doi.org/10.1038/cr.2008.282.
Cheng, L., Doecke, J. D., Sharples, R. A., Villemagne, V. L., Fowler, C. J., Rembach, A., et al. (2015). Prognostic serum miRNA biomarkers associated with Alzheimer's disease shows concordance with neuropsychological and neuroimaging assessment. *Molecular Psychiatry, 20*(10), 1188–1196. https://doi.org/10.1038/mp.2014.127.
Chien, D. T., Bahri, S., Szardenings, A. K., Walsh, J. C., Mu, F., Su, M. Y., et al. (2013). Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. *Journal of Alzheimers Disease, 34*(2), 457–468. https://doi.org/10.3233/JAD-122059.
Chiti, F., & Dobson, C. M. (2017). Protein misfolding, amyloid formation, and human disease: A summary of progress over the last decade. *Annual Review of Biochemistry, 86,* 27–68. https://doi.org/10.1146/annurev-biochem-061516-045115.

Cogswell, J. P., Ward, J., Taylor, I. A., Waters, M., Shi, Y., Cannon, B., et al. (2008). Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. *Journal of Alzheimers Disease, 14*(1), 27–41.

Cosin-Tomas, M., Antonell, A., Llado, A., Alcolea, D., Fortea, J., Ezquerra, M., et al. (2017). Plasma miR-34a-5p and miR-545-3p as early biomarkers of alzheimer's disease: Potential and limitations. *Molecular Neurobiology, 54*(7), 5550–5562. https://doi.org/10.1007/s12035-016-0088-8.

Davidson, Y. S., Robinson, A., Prasher, V. P., & Mann, D. M. A. (2018). The age of onset and evolution of Braak tangle stage and Thal amyloid pathology of Alzheimer's disease in individuals with Down syndrome. *Acta Neuropathologica Communications, 6*(1), 56. https://doi.org/10.1186/s40478-018-0559-4.

Davis, J., Xu, F., Hatfield, J., Lee, H., Hoos, M. D., Popescu, D., et al. (2018). A novel transgenic rat model of robust cerebral microvascular amyloid with prominent vasculopathy. *American Journal of Pathology, 188*(12), 2877–2889. https://doi.org/10.1016/j.ajpath.2018.07.030.

Denk, J., Boelmans, K., Siegismund, C., Lassner, D., Arlt, S., & Jahn, H. (2015). MicroRNA profiling of CSF reveals potential biomarkers to detect Alzheimer`s disease. *PLoS ONE, 10*(5), e0126423. https://doi.org/10.1371/journal.pone.0126423.

Dobson, C. M. (1999). Protein misfolding, evolution and disease. *Trends in Biochemical Sciences, 24*(9), 329–332.

Dong, H., Li, J., Huang, L., Chen, X., Li, D., Wang, T., et al. (2015). Serum MicroRNA profiles serve as novel biomarkers for the diagnosis of alzheimer's disease. *Disease Markers, 2015,* 625659. https://doi.org/10.1155/2015/625659.

Donohue, M. C., Jacqmin-Gadda, H., Le Goff, M., Thomas, R. G., Raman, R., Gamst, A. C., et al. (2014). Estimating long-term multivariate progression from short-term data. *Alzheimers Dement, 10*(5 Suppl), S400–S410. https://doi.org/10.1016/j.jalz.2013.10.003.

Du, X., Huo, X., Yang, Y., Hu, Z., Botchway, B. O. A., Jiang, Y., et al. (2017). miR-124 downregulates BACE 1 and alters autophagy in APP/PS1 transgenic mice. *Toxicology Letters, 280,* 195–205. https://doi.org/10.1016/j.toxlet.2017.08.082.

Elder, G. A., Gama Sosa, M. A., & De Gasperi, R. (2010). Transgenic mouse models of Alzheimer's disease. *Mount Sinai Journal of Medicine, 77*(1), 69–81. https://doi.org/10.1002/msj.20159.

Filipowicz, W., Bhattacharyya, S. N., & Sonenberg, N. (2008). Mechanisms of post-transcriptional regulation by microRNAs: Are the answers in sight? *Nature Reviews Genetics, 9*(2), 102–114. https://doi.org/10.1038/nrg2290.

Fink, A. L. (1998). Protein aggregation: Folding aggregates, inclusion bodies and amyloid. *Folding and Design, 3*(1), R9–R23. https://doi.org/10.1016/S1359-0278(98)00002-9.

Fleisher, A. S., Chen, K., Liu, X., Roontiva, A., Thiyyagura, P., Ayutyanont, N., et al. (2011). Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Archives of Neurology, 68*(11), 1404–1411. https://doi.org/10.1001/archneurol.2011.150.

Fleisher, A. S., Chen, K., Quiroz, Y. T., Jakimovich, L. J., Gutierrez Gomez, M., Langois, C. M., et al. (2015). Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study. *JAMA Neurology, 72*(3), 316–324. https://doi.org/10.1001/jamaneurol.2014.3314.

Forstl, H., & Kurz, A. (1999). Clinical features of Alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience, 249*(6), 288–290.

Galimberti, D., Villa, C., Fenoglio, C., Serpente, M., Ghezzi, L., Cioffi, S. M., et al. (2014). Circulating miRNAs as potential biomarkers in Alzheimer's disease. *Journal of Alzheimers Disease, 42*(4), 1261–1267. https://doi.org/10.3233/JAD-140756.

Gantier, M. P., McCoy, C. E., Rusinova, I., Saulep, D., Wang, D., Xu, D., et al. (2011). Analysis of microRNA turnover in mammalian cells following Dicer1 ablation. *Nucleic Acids Research, 39*(13), 5692–5703. https://doi.org/10.1093/nar/gkr148.

Geekiyanage, H., Jicha, G. A., Nelson, P. T., & Chan, C. (2012). Blood serum miRNA: Non-invasive biomarkers for Alzheimer's disease. *Experimental Neurology, 235*(2), 491–496. https://doi.org/10.1016/j.expneurol.2011.11.026.

Giraldez, A. J., Cinalli, R. M., Glasner, M. E., Enright, A. J., Thomson, J. M., Baskerville, S., et al. (2005). MicroRNAs regulate brain morphogenesis in zebrafish. *Science, 308*(5723), 833–838. https://doi.org/10.1126/science.1109020.

Glabe, C. G. (2006). Common mechanisms of amyloid oligomer pathogenesis in degenerative disease. *Neurobiology of Aging, 27*(4), 570–575. https://doi.org/10.1016/j.neurobiolaging.2005.04.017.

Goodall, E. F., Heath, P. R., Bandmann, O., Kirby, J., & Shaw, P. J. (2013). Neuronal dark matter: the emerging role of microRNAs in neurodegeneration. *Frontiers in Cellular Neuroscience, 7,* 178. https://doi.org/10.3389/fncel.2013.00178.

Grasso, M., Piscopo, P., Confaloni, A., & Denti, M. A. (2014). Circulating miRNAs as biomarkers for neurodegenerative disorders. *Molecules, 19*(5), 6891–6910. https://doi.org/10.3390/molecules19056891.

Greenberg, S. M., & Charidimou, A. (2018). Diagnosis of cerebral amyloid angiopathy: Evolution of the Boston criteria. *Stroke, 49*(2), 491–497. https://doi.org/10.1161/STROKEAHA.117.016990.

Gui, Y., Liu, H., Zhang, L., Lv, W., & Hu, X. (2015). Altered microRNA profiles in cerebrospinal fluid exosome in Parkinson disease and Alzheimer disease. *Oncotarget, 6*(35), 37043–37053. https://doi.org/10.18632/oncotarget.6158.

Hammond, S. M. (2015). An overview of microRNAs. *Advanced Drug Delivery Reviews, 87,* 3–14. https://doi.org/10.1016/j.addr.2015.05.001.

Hardy, J. (2006). Has the amyloid cascade hypothesis for Alzheimer's disease been proved? *Current Alzheimer Research, 3*(1), 71–73.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science, 297*(5580), 353–356. https://doi.org/10.1126/science.1072994.

He, D., Tan, J., & Zhang, J. (2017). miR-137 attenuates Abeta-induced neurotoxicity through inactivation of NF-kappaB pathway by targeting TNFAIP1 in Neuro2a cells. *Biochemical and Biophysical Research Communications, 490*(3), 941–947. https://doi.org/10.1016/j.bbrc.2017.06.144.

Hebert, S. S., Horre, K., Nicolai, L., Bergmans, B., Papadopoulou, A. S., Delacourte, A., et al. (2009). MicroRNA regulation of Alzheimer's Amyloid precursor protein expression. *Neurobiology of Diseases, 33*(3), 422–428. https://doi.org/10.1016/j.nbd.2008.11.009.

Hebert, S. S., Horre, K., Nicolai, L., Papadopoulou, A. S., Mandemakers, W., Silahtaroglu, A. N., et al. (2008). Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. *Proceedings of the National Academy of Sciences, 105*(17), 6415–6420. https://doi.org/10.1073/pnas.0710263105.

Hebert, S. S., Papadopoulou, A. S., Smith, P., Galas, M. C., Planel, E., Silahtaroglu, A. N., et al. (2010). Genetic ablation of Dicer in adult forebrain neurons results in abnormal tau hyperphosphorylation and neurodegeneration. *Human Molecular Genetics, 19*(20), 3959–3969. https://doi.org/10.1093/hmg/ddq311.

Helwak, A., Kudla, G., Dudnakova, T., & Tollervey, D. (2013). Mapping the human miRNA interactome by CLASH reveals

frequent noncanonical binding. *Cell, 153*(3), 654–665. https://doi.org/10.1016/j.cell.2013.03.043.

Hernandez-Rapp, J., Rainone, S., Goupil, C., Dorval, V., Smith, P. Y., Saint-Pierre, M., et al. (2016). microRNA-132/212 deficiency enhances Abeta production and senile plaque deposition in Alzheimer's disease triple transgenic mice. *Scientific Reports, 6,* 30953. https://doi.org/10.1038/srep30953.

Herzig, M. C., Winkler, D. T., Burgermeister, P., Pfeifer, M., Kohler, E., Schmidt, S. D., et al. (2004). Abeta is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. *Nature Neuroscience, 7*(9), 954–960. https://doi.org/10.1038/nn1302.

Higaki, S., Muramatsu, M., Matsuda, A., Matsumoto, K., Satoh, J. I., Michikawa, M., et al. (2018). Defensive effect of microRNA-200b/c against amyloid-beta peptide-induced toxicity in Alzheimer's disease models. *PLoS ONE, 13*(5), e0196929. https://doi.org/10.1371/journal.pone.0196929.

Hong, H., Li, Y., & Su, B. (2017). Identification of circulating miR-125b as a potential biomarker of Alzheimer's disease in APP/PS1 transgenic mouse. *Journal of Alzheimer's Disease, 59*(4), 1449–1458. https://doi.org/10.3233/JAD-170156.

Howe, M. D., Atadja, L. A., Furr, J. W., Maniskas, M. E., Zhu, L., McCullough, L. D., et al. (2018a). Fibronectin induces the perivascular deposition of cerebrospinal fluid-derived amyloid-beta in aging and after stroke. *Neurobiology of Aging, 72,* 1–13. https://doi.org/10.1016/j.neurobiolaging.2018.07.019.

Howe, M. D., Zhu, L., Sansing, L. H., Gonzales, N. R., McCullough, L. D., & Edwards, N. J. (2018b). Serum markers of blood-brain barrier remodeling and fibrosis as predictors of etiology and clinicoradiologic outcome in intracerebral hemorrhage. *Frontiers in Neurology, 9,* 746. https://doi.org/10.3389/fneur.2018.00746.

Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., et al. (1996). Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science, 274*(5284), 99–102.

Hsu, P. W., Huang, H. D., Hsu, S. D., Lin, L. Z., Tsou, A. P., Tseng, C. P., et al. (2006). miRNA Map: Genomic maps of microRNA genes and their target genes in mammalian genomes. *Nucleic Acids Research 34*(Database issue), D135-139, https://doi.org/10.1093/nar/gkj135.

Hu, S., Wang, H., Chen, K., Cheng, P., Gao, S., Liu, J., et al. (2015). MicroRNA-34c downregulation ameliorates amyloid-beta-induced synaptic failure and memory deficits by targeting VAMP2. *Journal of Alzheimers Disease, 48*(3), 673–686. https://doi.org/10.3233/JAD-150432.

Huang, Y., Shen, X. J., Zou, Q., Wang, S. P., Tang, S. M., & Zhang, G. Z. (2011). Biological functions of microRNAs: A review. *Journal of Physiology and Biochemistry, 67*(1), 129–139. https://doi.org/10.1007/s13105-010-0050-6.

Ikonomovic, M. D., Klunk, W. E., Abrahamson, E. E., Mathis, C. A., Price, J. C., Tsopelas, N. D., et al. (2008). Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain, 131*(Pt 6), 1630–1645. https://doi.org/10.1093/brain/awn016.

Iqbal, K., & Grundke-Iqbal, I. (2010). Alzheimer's disease, a multifactorial disorder seeking multitherapies. *Alzheimers Dement, 6*(5), 420–424. https://doi.org/10.1016/j.jalz.2010.04.006.

Jack, C. R., Jr., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., et al. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 257–262. https://doi.org/10.1016/j.jalz.2011.03.004.

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement, 14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018.

Jack, C. R., Jr., Lowe, V. J., Senjem, M. L., Weigand, S. D., Kemp, B. J., Shiung, M. M., et al. (2008). 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain, 131*(Pt 3), 665–680. https://doi.org/10.1093/brain/awm336.

Jankowsky, J. L., Fadale, D. J., Anderson, J., Xu, G. M., Gonzales, V., Jenkins, N. A., et al. (2004). Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: Evidence for augmentation of a 42-specific gamma secretase. *Human Molecular Genetics, 13*(2), 159–170. https://doi.org/10.1093/hmg/ddh019.

Jankowsky, J. L., Slunt, H. H., Ratovitski, T., Jenkins, N. A., Copeland, N. G., & Borchelt, D. R. (2001). Co-expression of multiple transgenes in mouse CNS: A comparison of strategies. *Biomolecular Engineering, 17*(6), 157–165.

Jawhar, S., Trawicka, A., Jenneckens, C., Bayer, T. A., & Wirths, O. (2012). Motor deficits, neuron loss, and reduced anxiety coinciding with axonal degeneration and intraneuronal Aβ aggregation in the 5XFAD mouse model of Alzheimer's disease. *Neurobiology of Aging, 33*(1), 196.e29–196.e140. https://doi.org/10.1016/j.neurobiolaging.2010.05.027.

Jiang, Y., Xu, B., Chen, J., Sui, Y., Ren, L., Li, J., et al. (2018). Micro-RNA-137 inhibits Tau hyperphosphorylation in Alzheimer's disease and targets the CACNA1C gene in transgenic mice and human neuroblastoma SH-SY5Y cells. *Medical Science Monitor, 24,* 5635–5644. https://doi.org/10.12659/MSM.908765.

Johnson, K. A., Sperling, R. A., Gidicsin, C. M., Carmasin, J. S., Maye, J. E., Coleman, R. E., et al. (2013). Florbetapir (F18-AV-45) PET to assess amyloid burden in Alzheimer's disease dementia, mild cognitive impairment, and normal aging. *Alzheimers Dement, 9*(5 Suppl), S72–S83. https://doi.org/10.1016/j.jalz.2012.10.007.

Kayano, M., Higaki, S., Satoh, J. I., Matsumoto, K., Matsubara, E., Takikawa, O., et al. (2016). Plasma microRNA biomarker detection for mild cognitive impairment using differential correlation analysis. *Biomarker Research, 4,* 22. https://doi.org/10.1186/s40364-016-0076-1.

Kiko, T., Nakagawa, K., Tsuduki, T., Furukawa, K., Arai, H., & Miyazawa, T. (2014). MicroRNAs in plasma and cerebrospinal fluid as potential markers for Alzheimer's disease. *Journal of Alzheimers Disease, 39*(2), 253–259. https://doi.org/10.3233/JAD-130932.

Knopman, D. S., Haeberlein, S. B., Carrillo, M. C., Hendrix, J. A., Kerchner, G., Margolin, R., et al. (2018). The National Institute on Aging and the Alzheimer's Association Research framework for Alzheimer's disease: Perspectives from the research roundtable. *Alzheimers Dement, 14*(4), 563–575. https://doi.org/10.1016/j.jalz.2018.03.002.

Knopman, D. S., Jack, C. R., Jr., Wiste, H. J., Weigand, S. D., Vemuri, P., Lowe, V. J., et al. (2013). Brain injury biomarkers are not dependent on β-amyloid in normal elderly. *Annals of Neurology, 73*(4), 472–480. https://doi.org/10.1002/ana.23816.

Knudsen, K. A., Rosand, J., Karluk, D., & Greenberg, S. M. (2001). Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston criteria. *Neurology, 56*(4), 537–539.

Kosik, K. S., & Krichevsky, A. M. (2005). The elegance of the MicroRNAs: A neuronal perspective. *Neuron, 47*(6), 779–782. https://doi.org/10.1016/j.neuron.2005.08.019.

Kumar, S., Reddy, A. P., Yin, X., & Reddy, P. H. (2019). Novel MicroRNA-455-3p and its protective effects against abnormal APP processing and amyloid beta toxicity in Alzheimer's disease. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1865*(9), 2428–2440. https://doi.org/10.1016/j.bbadis.2019.06.006.

Kumar, S., Vijayan, M., & Reddy, P. H. (2017). MicroRNA-455-3p as a potential peripheral biomarker for Alzheimer's disease. *Human Molecular Genetics, 26*(19), 3808–3822. https://doi.org/10.1093/hmg/ddx267.

Lee, K., Kim, H., An, K., Kwon, O. B., Park, S., Cha, J. H., et al. (2016). Replenishment of microRNA-188-5p restores the synaptic and cognitive deficits in 5XFAD mouse model of Alzheimer's disease. *Scientific Reports, 6,* 34433. https://doi.org/10.1038/srep34433.

Lei, X., Lei, L., Zhang, Z., Zhang, Z., & Cheng, Y. (2015). Downregulated miR-29c correlates with increased BACE1 expression in sporadic Alzheimer's disease. *International Journal of Clinical and Experimental Pathology, 8*(2), 1565–1574.

Leidinger, P., Backes, C., Deutscher, S., Schmitt, K., Mueller, S. C., Frese, K., et al. (2013). A blood based 12-miRNA signature of Alzheimer disease patients. *Genome Biology, 14*(7), R78. https://doi.org/10.1186/gb-2013-14-7-r78.

Lemere, C. A., Blusztajn, J. K., Yamaguchi, H., Wisniewski, T., Saido, T. C., & Selkoe, D. J. (1996). Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: Implications for initial events in amyloid plaque formation. *Neurobiology of Diseases, 3*(1), 16–32. https://doi.org/10.1006/nbdi.1996.0003.

Lennox, K. A., & Behlke, M. A. (2010). A direct comparison of anti-microRNA oligonucleotide potency. *Pharmaceutical Research, 27*(9), 1788–1799. https://doi.org/10.1007/s11095-010-0156-0.

Lewis, B. P., Burge, C. B., & Bartel, D. P. (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell, 120*(1), 15–20. https://doi.org/10.1016/j.cell.2004.12.035.

Li, H. H., Lin, S. L., Huang, C. N., Lu, F. J., Chiu, P. Y., Huang, W. N., et al. (2016). miR-302 Attenuates Amyloid-beta-Induced Neurotoxicity through Activation of Akt Signaling. *Journal of Alzheimers Disease, 50*(4), 1083–1098. https://doi.org/10.3233/JAD-150741.

Li, J., & Wang, H. (2018). miR-15b reduces amyloid-beta accumulation in SH-SY5Y cell line through targeting NF-kappaB signaling and BACE1. *Bioscience Reports*. https://doi.org/10.1042/BSR20180051.

Liang, C., Zhu, H., Xu, Y., Huang, L., Ma, C., Deng, W., et al. (2012). MicroRNA-153 negatively regulates the expression of amyloid precursor protein and amyloid precursor-like protein 2. *Brain Research, 1455,* 103–113. https://doi.org/10.1016/j.brainres.2011.10.051.

Lim, L. P., Lau, N. C., Garrett-Engele, P., Grimson, A., Schelter, J. M., Castle, J., et al. (2005). Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature, 433*(7027), 769–773. https://doi.org/10.1038/nature03315.

Liu, W., Liu, C., Zhu, J., Shu, P., Yin, B., Gong, Y., et al. (2012). MicroRNA-16 targets amyloid precursor protein to potentially modulate Alzheimer's-associated pathogenesis in SAMP8 mice. *Neurobiology of Aging, 33*(3), 522–534. https://doi.org/10.1016/j.neurobiolaging.2010.04.034.

Liu, C. G., Wang, J. L., Li, L., & Wang, P. C. (2014a). MicroRNA-384 regulates both amyloid precursor protein and beta-secretase expression and is a potential biomarker for Alzheimer's disease. *International Journal of Molecular Medicine, 34*(1), 160–166. https://doi.org/10.3892/ijmm.2014.1780.

Liu, C. G., Wang, J. L., Li, L., Xue, L. X., Zhang, Y. Q., & Wang, P. C. (2014b). MicroRNA-135a and -200b, potential biomarkers for Alzheimers disease, regulate beta secretase and amyloid precursor protein. *Brain Research, 1583,* 55–64. https://doi.org/10.1016/j.brainres.2014.04.026.

Liu, C. D., Wang, Q., Zong, D. K., Pei, S. C., Yan, Y., Yan, M. L., et al. (2016a). Knockdown of microRNA-195 contributes to protein phosphatase-2A inactivation in rats with chronic brain hypoperfusion. *Neurobiology of Aging, 45,* 76–87. https://doi.org/10.1016/j.neurobiolaging.2016.05.010.

Liu, W., Zhao, J., & Lu, G. (2016b). miR-106b inhibits tau phosphorylation at Tyr18 by targeting Fyn in a model of Alzheimer's disease. *Biochemical and Biophysical Research Communications, 478*(2), 852–857. https://doi.org/10.1016/j.bbrc.2016.08.037.

Londin, E., Loher, P., Telonis, A. G., Quann, K., Clark, P., Jing, Y., et al. (2015). Analysis of 13 cell types reveals evidence for the expression of numerous novel primate- and tissue-specific microRNAs. *Proceedings of the National Academy of Sciences USA, 112*(10), E1106–E1115. https://doi.org/10.1073/pnas.1420955112.

Long, J. M., Ray, B., & Lahiri, D. K. (2012). MicroRNA-153 physiologically inhibits expression of amyloid-beta precursor protein in cultured human fetal brain cells and is dysregulated in a subset of Alzheimer disease patients. *Journal of Biological Chemistry, 287*(37), 31298–31310. https://doi.org/10.1074/jbc.M112.366336.

Lukiw, W. J. (2007). Micro-RNA speciation in fetal, adult and Alzheimer's disease hippocampus. *NeuroReport, 18*(3), 297–300. https://doi.org/10.1097/WNR.0b013e3280148e8b.

Lukiw, W. J., Zhao, Y., & Cui, J. G. (2008). An NF-kappaB-sensitive micro RNA-146a-mediated inflammatory circuit in Alzheimer disease and in stressed human brain cells. *Journal of Biological Chemistry, 283*(46), 31315–31322. https://doi.org/10.1074/jbc.M805371200.

Marras, C., Beck, J. C., Bower, J. H., Roberts, E., Ritz, B., Ross, G. W., et al. (2018). Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Diseases, 4,* 21. https://doi.org/10.1038/s41531-018-0058-0.

Martin, I., Dawson, V. L., & Dawson, T. M. (2011). Recent advances in the genetics of Parkinson's disease. *Annual Review of Genomics and Human Genetics, 12,* 301–325. https://doi.org/10.1146/annurev-genom-082410-101440.

Martinez, B., & Peplow, P. V. (2019). MicroRNAs as diagnostic and therapeutic tools for Alzheimer's disease: Advances and limitations. *Neural Regeneration Research, 14*(2), 242–255. https://doi.org/10.4103/1673-5374.244784.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005.

Mead, S., & Reilly, M. M. (2015). A new prion disease: Relationship with central and peripheral amyloidoses. *Nature Reviews Neurology, 11*(2), 90–97. https://doi.org/10.1038/nrneurol.2014.263.

Millan, M. J. (2017). Linking deregulation of non-coding RNA to the core pathophysiology of Alzheimer's disease: An integrative review. *Progress in Neurobiology, 156,* 1–68. https://doi.org/10.1016/j.pneurobio.2017.03.004.

Mintun, M. A., Larossa, G. N., Sheline, Y. I., Dence, C. S., Lee, S. Y., Mach, R. H., et al. (2006). [11C]PIB in a nondemented population: Potential antecedent marker of Alzheimer disease. *Neurology, 67*(3), 446–452. https://doi.org/10.1212/01.wnl.0000228230.26044.a4.

Miya Shaik, M., Tamargo, I. A., Abubakar, M. B., Kamal, M. A., Greig, N. H., & Gan, S. H. (2018). The role of microRNAs in Alzheimer's disease and their therapeutic potentials. *Genes (Basel)*. https://doi.org/10.3390/genes9040174.

Mohr, A. M., & Mott, J. L. (2015). Overview of microRNA biology. *Seminars in Liver Disease, 35*(1), 3–11. https://doi.org/10.1055/s-0034-1397344.

Moreno-Gonzalez, I., & Soto, C. (2011). Misfolded protein aggregates: mechanisms, structures and potential for disease transmission.

Seminars in Cell & Developmental Biology, 22(5), 482–487. https://doi.org/10.1016/j.semcdb.2011.04.002.

Mormino, E. C., Betensky, R. A., Hedden, T., Schultz, A. P., Amariglio, R. E., Rentz, D. M., et al. (2014). Synergistic effect of beta-amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurology, 71*(11), 1379–1385. https://doi.org/10.1001/jamaneurol.2014.2031.

Morris, J. C., & Cummings, J. (2005). Mild cognitive impairment (MCI) represents early-stage Alzheimer's disease. *Journal of Alzheimers Disease, 7*(3), 235–239. **discussion 255-262**.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., et al. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology, 58*(3), 397–405.

Mukherjee, A., Morales-Scheihing, D., Butler, P. C., & Soto, C. (2015). Type 2 diabetes as a protein misfolding disease. *Trends in Molecular Medicine, 21*(7), 439–449. https://doi.org/10.1016/j.molmed.2015.04.005.

Mukherjee, A., Morales-Scheihing, D., Salvadores, N., Moreno-Gonzalez, I., Gonzalez, C., Taylor-Presse, K., et al. (2017). Induction of IAPP amyloid deposition and associated diabetic abnormalities by a prion-like mechanism. *Journal of Experimental Medicine, 214*(9), 2591–2610. https://doi.org/10.1084/jem.20161134.

Mullard, A. (2019). Pioneering antisense drug heads into pivotal trials for Huntington disease. *Nature Reviews Drug Discovery, 18*(3), 161–163. https://doi.org/10.1038/d41573-019-00018-7.

Muller, M., Jakel, L., Bruinsma, I. B., Claassen, J. A., Kuiperij, H. B., & Verbeek, M. M. (2016a). MicroRNA-29a is a candidate biomarker for Alzheimer's disease in cell-free cerebrospinal fluid. *Molecular Neurobiology, 53*(5), 2894–2899. https://doi.org/10.1007/s12035-015-9156-8.

Muller, M., Kuiperij, H. B., Claassen, J. A., Kusters, B., & Verbeek, M. M. (2014). MicroRNAs in Alzheimer's disease: Differential expression in hippocampus and cell-free cerebrospinal fluid. *Neurobiology of Aging, 35*(1), 152–158. https://doi.org/10.1016/j.neurobiolaging.2013.07.005.

Muller, M., Kuiperij, H. B., Versleijen, A. A., Chiasserini, D., Farotti, L., Baschieri, F., et al. (2016b). Validation of microRNAs in cerebrospinal fluid as biomarkers for different forms of dementia in a multicenter study. *Journal of Alzheimers Disease, 52*(4), 1321–1333. https://doi.org/10.3233/JAD-160038.

Nelson, P. T., Head, E., Schmitt, F. A., Davis, P. R., Neltner, J. H., Jicha, G. A., et al. (2011). Alzheimer's disease is not "brain aging": Neuropathological, genetic, and epidemiological human studies. *Acta Neuropathologica, 121*(5), 571–587. https://doi.org/10.1007/s00401-011-0826-y.

Nelson, P. T., & Keller, J. N. (2007). RNA in brain disease: No longer just "the messenger in the middle". *Journal of Neuropathology and Experimental Neurology, 66*(6), 461–468. https://doi.org/10.1097/01.jnen.0000240474.27791.f3.

Nelson, P., Kiriakidou, M., Sharma, A., Maniataki, E., & Mourelatos, Z. (2003). The microRNA world: Small is mighty. *Trends in Biochemical Sciences, 28*(10), 534–540. https://doi.org/10.1016/j.tibs.2003.08.005.

Nicolas, G., Wallon, D., Goupil, C., Richard, A. C., Pottier, C., Dorval, V., et al. (2016). Mutation in the 3′untranslated region of APP as a genetic determinant of cerebral amyloid angiopathy. *European Journal of Human Genetics, 24*(1), 92–98. https://doi.org/10.1038/ejhg.2015.61.

Nixon, R. A. (2013). The role of autophagy in neurodegenerative disease. *Nature Medicine, 19*(8), 983–997. https://doi.org/10.1038/nm.3232.

Nunez-Iglesias, J., Liu, C. C., Morgan, T. E., Finch, C. E., & Zhou, X. J. (2010). Joint genome-wide profiling of miRNA and mRNA expression in Alzheimer's disease cortex reveals altered miRNA regulation. *PLoS ONE, 5*(2), e8898. https://doi.org/10.1371/journal.pone.0008898.

Patel, N., Hoang, D., Miller, N., Ansaloni, S., Huang, Q., Rogers, J. T., et al. (2008). MicroRNAs can regulate human APP levels. *Molecular Neurodegeneration, 3,* 10. https://doi.org/10.1186/1750-1326-3-10.

Petrov, D., Mansfield, C., Moussy, A., & Hermine, O. (2017). ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment? *Frontiers in Aging Neuroscience, 9,* 68. https://doi.org/10.3389/fnagi.2017.00068.

Prestia, A., Caroli, A., van der Flier, W. M., Ossenkoppele, R., Van Berckel, B., Barkhof, F., et al. (2013). Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology, 80*(11), 1048–1056. https://doi.org/10.1212/WNL.0b013e3182872830.

Price, J. L., Davis, P. B., Morris, J. C., & White, D. L. (1991). The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. *Neurobiology of Aging, 12*(4), 295–312.

Prusiner, S. B. (1982). Novel proteinaceous infectious particles cause scrapie. *Science, 216*(4542), 136–144.

Prusiner, S. B. (1998). Prions. *Proceedings of the National Academy of Sciences, 95*(23), 13363–13383.

Rabinovici, G. D., Jagust, W. J., Furst, A. J., Ogar, J. M., Racine, C. A., Mormino, E. C., et al. (2008). Abeta amyloid and glucose metabolism in three variants of primary progressive aphasia. *Annals of Neurology, 64*(4), 388–401. https://doi.org/10.1002/ana.21451.

Reddy, P. H., Tripathi, R., Troung, Q., Tirumala, K., Reddy, T. P., Anekonda, V., et al. (2012). Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: Implications to mitochondria-targeted antioxidant therapeutics. *Biochimica et Biophysica Acta, 1822*(5), 639–649. https://doi.org/10.1016/j.bbadis.2011.10.011.

Revesz, T., Holton, J. L., Lashley, T., Plant, G., Rostagno, A., Ghiso, J., et al. (2002). Sporadic and familial cerebral amyloid angiopathies. *Brain Pathology, 12*(3), 343–357.

Riancho, J., Vazquez-Higuera, J. L., Pozueta, A., Lage, C., Kazimierczak, M., Bravo, M., et al. (2017). MicroRNA profile in patients with Alzheimer's disease: Analysis of miR-9-5p and miR-598 in raw and exosome enriched cerebrospinal fluid samples. *Journal of Alzheimers Disease, 57*(2), 483–491. https://doi.org/10.3233/JAD-161179.

Richard, B. C., Kurdakova, A., Baches, S., Bayer, T. A., Weggen, S., & Wirths, O. (2015). Gene dosage dependent aggravation of the neurological phenotype in the 5XFAD mouse model of alzheimer's disease. *Journal of Alzheimers Disease, 45*(4), 1223–1236. https://doi.org/10.3233/JAD-143120.

Richards, J. G., Higgins, G. A., Ouagazzal, A. M., Ozmen, L., Kew, J. N., Bohrmann, B., et al. (2003). PS2APP transgenic mice, coexpressing hPS2mut and hAPPswe, show age-related cognitive deficits associated with discrete brain amyloid deposition and inflammation. *Journal of Neuroscience, 23*(26), 8989–9003.

Rodrigue, K. M., Kennedy, K. M., Devous, M. D., Sr., Rieck, J. R., Hebrank, A. C., Diaz-Arrastia, R., et al. (2012). β-Amyloid burden in healthy aging: Regional distribution and cognitive consequences. *Neurology, 78*(6), 387–395. https://doi.org/10.1212/WNL.0b013e318245d295.

Rowe, C. C., Bourgeat, P., Ellis, K. A., Brown, B., Lim, Y. Y., Mulligan, R., et al. (2013). Predicting Alzheimer disease with beta-amyloid imaging: Results from the Australian imaging, biomarkers, and lifestyle study of ageing. *Annals of Neurology, 74*(6), 905–913. https://doi.org/10.1002/ana.24040.

Rowe, C. C., Ellis, K. A., Rimajova, M., Bourgeat, P., Pike, K. E., Jones, G., et al. (2010). Amyloid imaging results from the Australian imaging, biomarkers and lifestyle (AIBL) study of

aging. *Neurobiology of Aging, 31*(8), 1275–1283. https://doi.org/10.1016/j.neurobiolaging.2010.04.007.

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., et al. (2007). Imaging β-amyloid burden in aging and dementia. *Neurology, 68*(20), 1718–1725. https://doi.org/10.1212/01.wnl.0000261919.22630.ea.

Rubinsztein, D. C., Codogno, P., & Levine, B. (2012). Autophagy modulation as a potential therapeutic target for diverse diseases. *Nature Reviews Drug Discovery, 11*(9), 709–730. https://doi.org/10.1038/nrd3802.

Salta, E., Sierksma, A., Vanden Eynden, E., & De Strooper, B. (2016). miR-132 loss de-represses ITPKB and aggravates amyloid and TAU pathology in Alzheimer's brain. *EMBO Molecular Medicine, 8*(9), 1005–1018. https://doi.org/10.15252/emmm.201606520.

Sarazin, M., de Souza, L. C., Lehericy, S., & Dubois, B. (2012). Clinical and research diagnostic criteria for Alzheimer's disease. *Neuroimaging Clinics N Am*. https://doi.org/10.1016/j.nic.2011.11.004.

Satoh, J., Kino, Y., & Niida, S. (2015). MicroRNA-Seq data analysis pipeline to identify blood biomarkers for alzheimer's disease from public data. *Biomarker Insights, 10,* 21–31. https://doi.org/10.4137/BMI.S25132.

Schipper, H. M., Maes, O. C., Chertkow, H. M., & Wang, E. (2007). MicroRNA expression in Alzheimer blood mononuclear cells. *Gene Regulation and Systems Biology, 1,* 263–274.

Schonrock, N., & Gotz, J. (2012). Decoding the non-coding RNAs in Alzheimer's disease. *Cellular and Molecular Life Sciences, 69*(21), 3543–3559. https://doi.org/10.1007/s00018-012-1125-z.

Schonrock, N., Ke, Y. D., Humphreys, D., Staufenbiel, M., Ittner, L. M., Preiss, T., et al. (2010). Neuronal microRNA deregulation in response to Alzheimer's disease amyloid-beta. *PLoS ONE, 5*(6), e11070. https://doi.org/10.1371/journal.pone.0011070.

Schratt, G. (2009). microRNAs at the synapse. *Nature Reviews Neuroscience, 10*(12), 842–849. https://doi.org/10.1038/nrn2763.

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine, 1*(1), a006189. https://doi.org/10.1101/cshperspect.a006189.

Shan, G., Li, Y., Zhang, J., Li, W., Szulwach, K. E., Duan, R., et al. (2008). A small molecule enhances RNA interference and promotes microRNA processing. *Nature Biotechnology, 26*(8), 933–940. https://doi.org/10.1038/nbt.1481.

Shioya, M., Obayashi, S., Tabunoki, H., Arima, K., Saito, Y., Ishida, T., et al. (2010). Aberrant microRNA expression in the brains of neurodegenerative diseases: miR-29a decreased in Alzheimer disease brains targets neurone navigator 3. *Neuropathology and Applied Neurobiology, 36*(4), 320–330. https://doi.org/10.1111/j.1365-2990.2010.01076.x.

Siegel, G., Obernosterer, G., Fiore, R., Oehmen, M., Bicker, S., Christensen, M., et al. (2009). A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. *Nature Cell Biology, 11*(6), 705–716. https://doi.org/10.1038/ncb1876.

Sierksma, A., Lu, A., Salta, E., Vanden Eynden, E., Callaerts-Vegh, Z., D'Hooge, R., et al. (2018). Deregulation of neuronal miRNAs induced by amyloid-beta or TAU pathology. *Molecular Neurodegeneration, 13*(1), 54. https://doi.org/10.1186/s13024-018-0285-1.

Simonson, B., & Das, S. (2015). MicroRNA therapeutics: The next magic bullet? *Mini Reviews in Medicinal Chemistry., 15*(6), 467–474.

Simpson, R. J., Lim, J. W., Moritz, R. L., & Mathivanan, S. (2009). Exosomes: Proteomic insights and diagnostic potential. *Expert Review of Proteomics, 6*(3), 267–283. https://doi.org/10.1586/epr.09.17.

Singer, O., Marr, R. A., Rockenstein, E., Crews, L., Coufal, N. G., Gage, F. H., et al. (2005). Targeting BACE1 with siRNAs ameliorates Alzheimer disease neuropathology in a transgenic model. *Nature Neuroscience, 8*(10), 1343–1349. https://doi.org/10.1038/nn1531.

Smith, P. Y., Delay, C., Girard, J., Papon, M. A., Planel, E., Sergeant, N., et al. (2011). MicroRNA-132 loss is associated with tau exon 10 inclusion in progressive supranuclear palsy. *Human Molecular Genetics, 20*(20), 4016–4024. https://doi.org/10.1093/hmg/ddr330.

Smith, P. Y., Hernandez-Rapp, J., Jolivette, F., Lecours, C., Bisht, K., Goupil, C., et al. (2015). miR-132/212 deficiency impairs tau metabolism and promotes pathological aggregation in vivo. *Human Molecular Genetics, 24*(23), 6721–6735. https://doi.org/10.1093/hmg/ddv377.

Soto, C. (2003). Unfolding the role of protein misfolding in neurodegenerative diseases. *Nature Reviews Neuroscience, 4*(1), 49–60. https://doi.org/10.1038/nrn1007.

Soto, C., Estrada, L., & Castilla, J. (2006). Amyloids, prions and the inherent infectious nature of misfolded protein aggregates. *Trends in Biochemical Sciences, 31*(3), 150–155. https://doi.org/10.1016/j.tibs.2006.01.002.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

Sturchler-Pierrat, C., Abramowski, D., Duke, M., Wiederhold, K. H., Mistl, C., Rothacher, S., et al. (1997). Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proceedings of the National Academy of Sciences USA, 94*(24), 13287–13292.

Sweeney, M. D., Montagne, A., Sagare, A. P., Nation, D. A., Schneider, L. S., Chui, H. C., et al. (2019). Vascular dysfunction-the disregarded partner of Alzheimer's disease. *Alzheimers Dement, 15*(1), 158–167. https://doi.org/10.1016/j.jalz.2018.07.222.

Tan, L., Yu, J. T., Liu, Q. Y., Tan, M. S., Zhang, W., Hu, N., et al. (2014). Circulating miR-125b as a biomarker of Alzheimer's disease. *Journal of the Neurological Sciences, 336*(1–2), 52–56. https://doi.org/10.1016/j.jns.2013.10.002.

Terrinoni, A., Calabrese, C., Basso, D., Aita, A., Caporali, S., Plebani, M., et al. (2018). The circulating miRNAs as diagnostic and prognostic markers. *Clinical Chemistry and Laboratory Medicine*. https://doi.org/10.1515/cclm-2018-0838.

Tiribuzi, R., Crispoltoni, L., Porcellati, S., Di Lullo, M., Florenzano, F., Pirro, M., et al. (2014). miR128 up-regulation correlates with impaired amyloid beta(1-42) degradation in monocytes from patients with sporadic Alzheimer's disease. *Neurobiology of Aging, 35*(2), 345–356. https://doi.org/10.1016/j.neurobiolaging.2013.08.003.

Toledo, J. B., Weiner, M. W., Wolk, D. A., Da, X., Chen, K., Arnold, S. E., et al. (2014). Neuronal injury biomarkers and prognosis in ADNI subjects with normal cognition. *Acta Neuropathologica Communications, 2,* 26. https://doi.org/10.1186/2051-5960-2-26.

Tomiyama, T., Matsuyama, S., Iso, H., Umeda, T., Takuma, H., Ohnishi, K., et al. (2010). A mouse model of amyloid beta oligomers: Their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss in vivo. *Journal of Neuroscience, 30*(14), 4845–4856. https://doi.org/10.1523/JNEUROSCI.5825-09.2010.

Toyama, K., Spin, J. M., & Tsao, P. S. (2017). Role of microRNAs on blood brain barrier dysfunction in vascular cognitive impairment. *Current Drug Delivery, 14*(6), 744–757. https://doi.org/10.2174/1567201813666160830124627.

Tsoi, H., Lau, T. C., Tsang, S. Y., Lau, K. F., & Chan, H. Y. (2012). CAG expansion induces nucleolar stress in polyglutamine diseases. *Proceedings of the National Academy of Sciences USA, 109*(33), 13428–13433. https://doi.org/10.1073/pnas.1204089109.

Uversky, V. N. (2007). Neuropathology, biochemistry, and biophysics of alpha-synuclein aggregation. *Journal of Neurochemistry, 103*(1), 17–37. https://doi.org/10.1111/j.1471-4159.2007.04764.x.

van Harten, A. C., Smits, L. L., Teunissen, C. E., Visser, P. J., Koene, T., Blankenstein, M. A., et al. (2013a). Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology, 81*(16), 1409–1416. https://doi.org/10.1212/WNL.0b013e3182a8418b.

van Harten, A. C., Visser, P. J., Pijnenburg, Y. A., Teunissen, C. E., Blankenstein, M. A., Scheltens, P., et al. (2013b). Cerebrospinal fluid Abeta42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimers Dement, 9*(5), 481–487. https://doi.org/10.1016/j.jalz.2012.08.004.

Vilardo, E., Barbato, C., Ciotti, M., Cogoni, C., & Ruberti, F. (2010). MicroRNA-101 regulates amyloid precursor protein expression in hippocampal neurons. *Journal of Biological Chemistry, 285*(24), 18344–18351. https://doi.org/10.1074/jbc.M110.112664.

Villemagne, V. L., Burnham, S., Bourgeat, P., Brown, B., Ellis, K. A., Salvado, O., et al. (2013). Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol, 12*(4), 357–367. https://doi.org/10.1016/S1474-4422(13)70044-9.

Villemagne, V. L., Fodero-Tavoletti, M. T., Masters, C. L., & Rowe, C. C. (2015). Tau imaging: Early progress and future directions. *Lancet Neurology, 14*(1), 114–124. https://doi.org/10.1016/S1474-4422(14)70252-2.

Visser, P. J., Verhey, F., Knol, D. L., Scheltens, P., Wahlund, L. O., Freund-Levi, Y., et al. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: A prospective cohort study. *Lancet Neurology, 8*(7), 619–627. https://doi.org/10.1016/S1474-4422(09)70139-5.

Walsh, D. M., & Selkoe, D. J. (2007). A beta oligomers - a decade of discovery. *Journal of Neurochemistry, 101*(5), 1172–1184. https://doi.org/10.1111/j.1471-4159.2006.04426.x.

Wang, T., Chen, K., Li, H., Dong, S., Su, N., Liu, Y., et al. (2015). The feasibility of utilizing plasma MiRNA107 and BACE1 messenger RNA gene expression for clinical diagnosis of amnestic mild cognitive impairment. *Journal of Clinical Psychiatry, 76*(2), 135–141. https://doi.org/10.4088/JCP.13m08812.

Wang, W. X., Huang, Q., Hu, Y., Stromberg, A. J., & Nelson, P. T. (2011). Patterns of microRNA expression in normal and early Alzheimer's disease human temporal cortex: White matter versus gray matter. *Acta Neuropathologica, 121*(2), 193–205. https://doi.org/10.1007/s00401-010-0756-0.

Wang, G., Huang, Y., Wang, L. L., Zhang, Y. F., Xu, J., Zhou, Y., et al. (2016). MicroRNA-146a suppresses ROCK1 allowing hyperphosphorylation of tau in Alzheimer's disease. *Scientific Reports, 6,* 26697. https://doi.org/10.1038/srep26697.

Wang, X., Liu, D., Huang, H. Z., Wang, Z. H., Hou, T. Y., Yang, X., et al. (2018). A novel MicroRNA-124/PTPN1 signal pathway mediates synaptic and memory deficits in Alzheimer's disease. *Biological Psychiatry, 83*(5), 395–405. https://doi.org/10.1016/j.biopsych.2017.07.023.

Wang, W. X., Rajeev, B. W., Stromberg, A. J., Ren, N., Tang, G., Huang, Q., et al. (2008). The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1. *Journal of Neuroscience, 28*(5), 1213–1223. https://doi.org/10.1523/JNEUROSCI.5065-07.2008.

Westermark, P., Andersson, A., & Westermark, G. T. (2011). Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. *Physiological Reviews, 91*(3), 795–826. https://doi.org/10.1152/physrev.00042.2009.

Williams, A., Sarkar, S., Cuddon, P., Ttofi, E. K., Saiki, S., Siddiqi, F. H., et al. (2008). Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. *Nature Chemical Biology, 4*(5), 295–305. https://doi.org/10.1038/nchembio.79.

Wirth, M., Madison, C. M., Rabinovici, G. D., Oh, H., Landau, S. M., & Jagust, W. J. (2013). Alzheimer's disease neurodegenerative biomarkers are associated with decreased cognitive function but not beta-amyloid in cognitively normal older individuals. *Journal of Neuroscience, 33*(13), 5553–5563. https://doi.org/10.1523/JNEUROSCI.4409-12.2013.

Wiseman, F. K., Al-Janabi, T., Hardy, J., Karmiloff-Smith, A., Nizetic, D., Tybulewicz, V. L., et al. (2015). A genetic cause of Alzheimer disease: Mechanistic insights from Down syndrome. *Nature Reviews Neuroscience, 16*(9), 564–574. https://doi.org/10.1038/nrn3983.

Wolfe, M. S. (2014). Targeting mRNA for Alzheimer's and related dementias. *Scientifica (Cairo), 2014,* 757549. https://doi.org/10.1155/2014/757549.

Wu, B. W., Wu, M. S., & Guo, J. D. (2018). Effects of microRNA-10a on synapse remodeling in hippocampal neurons and neuronal cell proliferation and apoptosis through the BDNF-TrkB signaling pathway in a rat model of Alzheimer's disease. *Journal of Cellular Physiology, 233*(7), 5281–5292. https://doi.org/10.1002/jcp.26328.

Wu, Y., Xu, J., Xu, J., Cheng, J., Jiao, D., Zhou, C., et al. (2017). Lower serum levels of miR-29c-3p and miR-19b-3p as biomarkers for Alzheimer's disease. *Tohoku Journal of Experimental Medicine, 242*(2), 129–136. https://doi.org/10.1620/tjem.242.129.

Xu, Y., Chen, P., Wang, X., Yao, J., & Zhuang, S. (2018). miR-34a deficiency in APP/PS1 mice promotes cognitive function by increasing synaptic plasticity via AMPA and NMDA receptors. *Neuroscience Letters, 670,* 94–104. https://doi.org/10.1016/j.neulet.2018.01.045.

Xu, N., Li, A. D., Ji, L. L., Ye, Y., Wang, Z. Y., & Tong, L. (2019). miR-132 regulates the expression of synaptic proteins in APP/PS1 transgenic mice through C1q. *European Journal of Histochemistry, 63*(2), 458. https://doi.org/10.4081/ejh.2019.3008.

Yang, L. B., Lindholm, K., Yan, R., Citron, M., Xia, W., Yang, X. L., et al. (2003). Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease. *Nature Medicine, 9*(1), 3–4. https://doi.org/10.1038/nm0103-3.

Yang, G., Song, Y., Zhou, X., Deng, Y., Liu, T., Weng, G., et al. (2015). MicroRNA-29c targets beta-site amyloid precursor protein-cleaving enzyme 1 and has a neuroprotective role in vitro and in vivo. *Molecular Medicine Reports, 12*(2), 3081–3088. https://doi.org/10.3892/mmr.2015.3728.

Yao, J., Hennessey, T., Flynt, A., Lai, E., Beal, M. F., & Lin, M. T. (2010). MicroRNA-related cofilin abnormality in Alzheimer's disease. *PLoS ONE, 5*(12), e15546. https://doi.org/10.1371/journal.pone.0015546.

Yilmaz, S. G., Erdal, M. E., Ozge, A. A., & Sungur, M. A. (2016). Can peripheral MicroRNA expression data serve as epigenomic (upstream) biomarkers of Alzheimer's disease? *OMICS: A Journal of Integrative Biology, 20*(8), 456–461. https://doi.org/10.1089/omi.2016.0099.

Young, A. L., Oxtoby, N. P., Daga, P., Cash, D. M., Fox, N. C., Ourselin, S., et al. (2014). A data-driven model of biomarker changes

in sporadic Alzheimer's disease. *Brain, 137*(Pt 9), 2564–2577. https://doi.org/10.1093/brain/awu176.

Zhang, B., Chen, C. F., Wang, A. H., & Lin, Q. F. (2015). MiR-16 regulates cell death in Alzheimer's disease by targeting amyloid precursor protein. *Eur Rev Med Pharmacol Sci, 19*(21), 4020–4027.

Zhang, Y., Li, Q., Liu, C., Gao, S., Ping, H., Wang, J., et al. (2016a). MiR-214-3p attenuates cognition defects via the inhibition of autophagy in SAMP8 mouse model of sporadic Alzheimer's disease. *Neurotoxicology, 56,* 139–149. https://doi.org/10.1016/j.neuro.2016.07.004.

Zhang, Y., Xing, H., Guo, S., Zheng, Z., Wang, H., & Xu, D. (2016b). MicroRNA-135b has a neuroprotective role via targeting of beta-site APP-cleaving enzyme 1. *Experimental and Therapeutic Medicine, 12*(2), 809–814. https://doi.org/10.3892/etm.2016.3366.

Zhang, J. A., Zhou, B. R., Xu, Y., Chen, X., Liu, J., Gozali, M., et al. (2016c). MiR-23a-depressed autophagy is a participant in PUVA- and UVB-induced premature senescence. *Oncotarget, 7*(25), 37420–37435. https://doi.org/10.18632/oncotarget.9357.

Zhao, Y., Zhao, R., Wu, J., Wang, Q., Pang, K., Shi, Q., et al. (2018). Melatonin protects against Abeta-induced neurotoxicity in primary neurons via miR-132/PTEN/AKT/FOXO3a pathway. *BioFactors, 44*(6), 609–618. https://doi.org/10.1002/biof.1411.

Zheng, H., Jiang, M., Trumbauer, M. E., Sirinathsinghji, D. J., Hopkins, R., Smith, D. W., et al. (1995). beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity. *Cell, 81*(4), 525–531.

Zhou, Y., Wang, Z. F., Li, W., Hong, H., Chen, J., Tian, Y., et al. (2018). Protective effects of microRNA-330 on amyloid beta-protein production, oxidative stress, and mitochondrial dysfunction in Alzheimer's disease by targeting VAV1 via the MAPK signaling pathway. *Journal of Cellular Biochemistry, 119*(7), 5437–5448. https://doi.org/10.1002/jcb.26700.

Zhu, H. C., Wang, L. M., Wang, M., Song, B., Tan, S., Teng, J. F., et al. (2012). MicroRNA-195 downregulates Alzheimer's disease amyloid-beta production by targeting BACE1. *Brain Research Bulletin, 88*(6), 596–601. https://doi.org/10.1016/j.brainresbull.2012.05.018.

Zipfel, G. J., Han, H., Ford, A. L., & Lee, J. M. (2009). Cerebral amyloid angiopathy: Progressive disruption of the neurovascular unit. *Stroke, 40*(3 Suppl), S16–S19. https://doi.org/10.1161/STROKEAHA.108.533174.

Zwan, M. D., Bouwman, F. H., Konijnenberg, E., van der Flier, W. M., Lammertsma, A. A., Verhey, F. R., et al. (2017). Diagnostic impact of [(18)F]flutemetamol PET in early-onset dementia. *Alzheimers Research Therapy, 9*(1), 2. https://doi.org/10.1186/s13195-016-0228-4.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.