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Review Article

MicroRNAs and Alzheimer's Disease Mouse Models: Current Insights and Future Research Avenues

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Evidence from clinical trials as well as from studies performed in animal models suggest that both amyloid and tau pathologies function in concert with other factors to cause the severe neurodegeneration and dementia in Alzheimer's disease (AD) patients. Accumulating data in the literature suggest that microRNAs (miRNAs) could be such factors. These conserved, small nonprotein-coding RNAs are essential for neuronal function and survival and have been implicated in the regulation of key genes involved in genetic and sporadic AD. The study of miRNA changes in AD mouse models provides an appealing approach to address the cause-consequence relationship between miRNA dysfunction and AD pathology in humans. Mouse models also provide attractive tools to validate miRNA targets *in vivo* and provide unique platforms to study the role of specific miRNA-dependent gene pathways in disease. Finally, mouse models may be exploited for miRNA diagnostics in the fight against AD.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia worldwide. It is characterized by the accumulation of extracellular amyloid (senile) plaques, composed mainly of Aβ peptides, and intracellular neurofibrillary tangles, containing abnormally aggregated and hyperphosphorylated Tau protein. The Aβ peptides are generated by the sequential cleavage of Amyloid precursor protein (APP) by β-secretase (BACE1-dependent) and γ-secretase (PSEN/presenilin-dependent). Based on the discovery of rare familial forms of AD caused mutations in the *APP* and *PSEN* genes, Hardy and Selkoe proposed the "amyloid cascade hypothesis", which suggests that Aβ overproduction alone is sufficient to trigger the molecular events leading to both tangle formation and neuronal cell death [1, 2]. Over the past two decades, several breakthroughs have been made with regard to modeling AD pathology *in vivo* in mice, providing important tools for various areas of basic and translational research. Several AD mouse models harboring human APP, PSEN, and/or MAPT (Tau) transgenes support to some extent the amyloid cascade hypothesis; however, recent clinical trials in humans suggest that amyloid-dependent signaling pathways are insufficient to cause the severe neurodegeneration and dementia in AD patients [3–5]. It is therefore perhaps not surprising that most, if not all, AD mouse models, albeit displaying massive Aβ deposits and/or tangles, do not recapitulate the full-blown neuropathological biochemical, cellular, and morphological changes observed in AD brain [6–8]. This opens the door to the identification of novel factors important for AD development, which could equally serve as potential diagnostic and therapeutic tools.

The past years have witnessed an explosion of papers linking microRNA (miRNA) dysfunction to human disease, including cancer, cardiology, liver disease, viral infection, and many others. Perhaps expectedly, mounting evidence also involve miRNAs in neurodegenerative disorders, with potential implications in AD [9, 10], Parkinson's disease (PD) [11], Huntington's disease (HD) [12, 13], frontotemporal dementia (FTD) [14, 15], and amyotrophic lateral sclerosis (ALS) [16]. Because of the rapid growth of miRNA research in general, it is likely other neurodegenerative disorders will soon be added to this list.

Recent RNA deep sequencing efforts have identified more than 1400 miRNA genes in the human genome (700 in mice) (miRBase.org). Several of these are specifically expressed in the brain, where they are proposed to function in neuronal processes such as neurite outgrowth and synapse formation [17, 18]. The biogenesis and mode of action of miRNA molecules in mammals is complex and has extensively been reviewed elsewhere (see, e.g., [19–22]). In short, miRNA precursors (pre-miRs) are cleaved in the cytoplasm by the RNase Dicer to produce small (~ 21 nt in length) single-stranded nonprotein-coding RNAs. These latter function as part of the RNA-induced silencing complex (RISC), which targets specific mRNA transcripts with imperfect complementarity. Binding of the miRNA to its target leads to translation inhibition and/or mRNA degradation [23, 24], which ultimately leads to down-regulation of the encoded protein. It is predicted that 25 to 70% of all protein-coding genes can be regulated by miRNAs, depending on the developmental, cellular, and/or physiological context. Moreover, each miRNA can target up to several hundred transcripts *in vivo*, thus potentially regulating multiple biological pathways, including those implicated in neuronal survival [25]. It is therefore not surprising that genetic ablation of *Dicer* in the brain, which leads to an overall reduction in miRNA production, results in rapid neurodegeneration [26–28].

The somewhat humble introduction of miRNAs in the AD field came in 2007 when Lukiw studied the expression levels of 13 brain miRNAs in control and AD patients, some of which were specifically altered in disease [29]. Since then, several groups have performed global miRNA expression analysis of AD brain [9, 10, 29–31] and peripheral system [32, 33]. These profiling experiments tend to show a trend towards the identification of "AD or neurodegenerative disease-specific" miRNAs, including miR-29, miR-9, miR-15a, miR-181c, miR-101, miR-106b, miR-146a, and miR-107, which have been identified in two or more independent studies. Interestingly, several of these miRNAs may have a direct role in modulating APP (miR-106, miR-101) [34–36] or BACE1 (miR-29, miR-107) [9, 37–39] expression, therefore potentially contributing to increase amyloid production. Because (1) miRNAs regulate APP and BACE1 expression, whose increased protein levels are linked to genetic and sporadic AD, respectively (reviewed in [21, 40]) and (2) miRNAs control several pathways involved in neuronal function, inflammation and survival, miRNA research provides an interesting new perspective to study the underlying mechanisms involved in AD development.

2. miRNA-Deficiency and the AD Brain

While depleting all miRNAs remain a conceptually crude approach, it is interesting to observe several parallels between *Dicer*-deficient brain and AD brain. For instance, neuronal *Dicer* conditional knockout (cKO) mice develop progressive neurodegeneration, have reduced brain size, enlarged ventricles, neuroinflammation, apoptosis (in some cases), as well as impaired dendritic branching, and spine length [26, 41, 42]. In addition, neuronal *Dicer* cKO mice exhibit AD-like hyperphosphorylation of endogenous tau [26], which is not observed in nontransgenic mice. These latter results succeed previous studies in the fly linking tau toxicity to miRNA dysfunction [43]. Interestingly, specific loss of *Dicer* in oligodendrocytes results in axonal degeneration accompanied by abnormal axonal transport and endogenous APP accumulation [44]. This model also displays signs of oxidative stress, and, taken together, these results point out the importance of Dicer and miRNAs in maintaining neuronal function. Although controversial, one study suggests that neuronal *Dicer* deficiency *promotes* learning and memory, at least at stages prior to neuronal loss [45]. How these observations translate to human disease remains speculative, but nevertheless provides "proof-of-principle" that loss (and perhaps gain) of brain miRNA function can participate in several neuropathological features of AD.

3. miRNA Profiles from AD Mice

Apart from the more obvious role of miRNAs in regulating the expression of disease-related genes (e.g., APP and BACE1), it is likely that a combination of more subtle (direct or indirect) mechanisms alter disease progression over years, possibly decades. As example, sustained miR-29 deficiency may not only increase BACE1 and Aβ levels, but also affect DNA methylation and neuronal survival [46, 47]. In addition, it remains difficult to predict whether the observed changes in miRNA levels in humans are a cause or consequence of the neurodegenerative process. The study of miRNA expression profiles in AD mouse models may help to address these questions.

Wang et al. were the first to study global miRNA profiles from AD mice using microarrays [48]. For this, they used the APPSwe-PS1M146L mouse model. Of the 37 differently expressed miRNAs, several (miR-20a, miR-29a, miR-125b, miR-128a, and miR-106b) miRNAs were significantly downregulated, while others (miR-34a, let-7, miR-28, and miR-98) were upregulated. Interestingly, some miRNAs were similarly shown to be affected in AD brain in humans, including miR-29a and miR-106b [9, 30, 31, 40, 49]. It is noteworthy that miRNA alterations were measured at 3 months of age prior to Aβ plaque formation. In most cases, miRNA alterations were maintained or even accentuated during amyloid plaque formation at 6 months of age, therefore supporting the "cause" hypothesis. The increase in miR-34a in the mutant mice is proposed to function in regulating apoptosis via Bcl-2 modulation [48]. In a follow-up study, the group showed by sensitive miRNA quantitative RT-PCR that miR-106b is upregulated in 3-month-old AD mice but downregulated at 6 months [50]. These changes correlated to some extent with transforming growth factor, beta receptor II (TβRII) expression, and a putative miR-106b target gene [50]. While these studies highlight the importance of microarray validation, they also suggest a possible transient effect of AD pathology (in this case Aβ plaque formation) on miRNA expression and vice versa.

More recently, Schonrock et al. studied the effects of exogenous Aβ on miRNA expression levels in mouse

hippocampal neurons in culture [51]. Again, several miRNAs downregulated by Aβ treatment were previously found to be decreased in human AD brain, including miR-9, miR-181c, miR-30c, miR-148b, miR-20b, and let-7i. Of interest, certain miRNAs decreased concomitantly with Aβ pathology progression *in vivo* in APP23 mice expressing human APP751 with the K670N/M671L mutations. While these observations support the "consequence" hypothesis of miRNA dysregulation in AD, it is noteworthy that some miRNA molecules became affected *prior* to Aβ plaque formation (like miR-409-3p and let-7i) similar to what is seen in the Wang et al. study ([48], see above). Furthermore, the expression of certain miRNAs changed over time (from up- to downregulated or vice versa), again supporting the transient effect on miRNA expression during AD development.

While studying the role of actin and the actin-binding protein cofilin in AD, Yao et al. observed decreased miR-103 and miR-107 levels in 4-month old (Aβ plaque bearing) Tg19959 mice that express mutant APP with KM670/671NL and V717F FAD mutations [52]. As mentioned above, both miR-103 and miR-107 were shown to be decreased in MCI and late-onset AD [10]. The authors further showed that these miRNA paralogues could effectively regulate cofilin expression *in vitro*, providing a mechanism for the observed increase in rod-like structures in this mouse model.

Loss of presenilin function is proposed to underlie memory impairment and neurodegeneration in the pathogenesis of AD [53]. Interestingly, small-scale miRNA profiling from Psen1 KO mice with, as a result, reduced γ-secretase activity and Aβ production, showed that miR-9 down-regulation coincided with neurodegeneration [54]. It is noteworthy that miR-9 was shown to be an important regulator of neurogenesis, both in zebrafish and mice [55, 56]. Based on these observations, it is tempting to speculate that miR-9, which is downregulated in AD brain, participates actively in neuronal maintenance, and functions in a feedback loop with Aβ.

Candidate miRNA approaches have equally been performed. For instance, Li et al. studied miR-146a expression in five different AD mouse models, including Tg-2576, Tg-CRND8, PSAPP, 3xTg-AD, and 5XFAD [57]. This group had shown earlier that miR-146a expression levels were increased in AD brain [58]. It turned out that miR-146a was significantly increased in age (4- to 12-month-old) when compared to young (1- to 2-month-old) mice, and this, independently of the model tested [57]. Notably, miR-146a has repeatedly been shown to be implicated in the regulation of the inflammatory response [59]. Moreover, neuroinflammation is thought to play a critical role in the pathogenesis of chronic neurodegenerative diseases including AD [60], evoking the hypothesis that miR-146a overexpression in these AD models could reflect a defense mechanism against the deleterious effects of neuroinflammation. Interestingly, synthetic Aβ was shown to induce miR-146a expression in cultured human neuronal (and glial) cells [58]. Taken together, the abovementioned observations suggest that miRNA-regulated gene pathways, such as the miR-146a pathway, could function both upstream and downstream of AD pathology (cause and consequence).

4. miRNA-Mediated Regulation of AD Genes *In Vivo*

One of the main challenges in the miRNA field is the identification of *bona fide* target genes. Several genome-wide methods are currently available to address this question, including microarray expression analyses following miRNA transfection/inhibition, Argonaute cross-linked immunoprecipitation (CLIP)-seq assays, and SILAC-based proteomic approaches [61–63]. So far, however, most miRNA studies involving AD-related genes have relied on artificial 3′UTR reporter systems (e.g., luciferase-based assays) as well as single miRNA gain- or loss-of-function experiments in cells. While these methods remain indispensable in the validation of miRNA : mRNA targets, they rarely put both molecules in their physiological context. In addition, it is important to consider that some miRNA:mRNA targets are not conserved in lower organisms such as *C. elegans* and Drosophila, making extrapolations to mammalian brain sometimes difficult (e.g., see [43]).

As of now, most studies addressing the role of miRNAs in AD gene regulation have focused on APP. These have lead to the identification of at least six miRNAs that could regulate APP *in vitro* and in cells, including the miR-20a family (i.e. miR-20a, miR-17-5p, and miR-106a/b), miR-101, and miR-16 [40, 64–68]. Interestingly, Liu et al. showed that miR-16 inhibition in 8-month-old SAMP8 mice, a model for accelerated senescence, reduced endogenous APP levels by ~50% [68]. Again, the effects on Aβ production remain to be determined. While providing the first "proof-of-principle" of APP regulation by miRNAs *in vivo*, this study does not exclude the role of other miRNAs in this process in the brain. For instance, our preliminary data indicate that APP mRNA levels are increased in miR-20a/17-5p double KO mice (Hebert, S.S., unpublished observations). In addition, it remains uncertain whether other miR-16 homologues, that is, miR-15a, miR-15b, miR-195, and miR-495 are involved in APP regulation *in vivo*. Interestingly, miR-16 family members have also been implicated in endogenous tau phosphorylation in neurons [26].

While investigating the molecular mechanisms involved in endogenous BACE1 overexpression in 6-month-old (Aβ plaque bearing) 5XFAD [69], O'Connor et al. observed no significant changes in miR-29a, miR-29b, and miR-9 levels, previously shown to regulate BACE1 *in vitro* [9], when compared to nontransgenic controls. Another study suggests however, that miR-29c (the third miR-29 family member) overexpression is sufficient to decrease endogenous BACE1 protein levels in wild-type mice [50]. The functional effects on BACE1 activity and Aβ production were unfortunately not evaluated in this latter model. Boissonneault et al. showed that BACE1 protein increases in 19-month-old (Aβ plaque bearing) versus 4-month-old APPSwe-PS1A246E mice [70], an effect not observed in wild-type mice. Interestingly, two miRNAs shown to regulate murine BACE1 expression *in vitro*, that is, miR-298 and miR-328 were downregulated in this mouse model. Whether other miRNAs are affected in the 5XFAD and APPSwe-PS1A246E mice remains to be determined. Lastly, Faghihi et al. showed that

BACE1 protein and BACE1 antisense (noncoding) transcript levels were increased in 6-week-old Tg19959 mice [71]. Whether decreased miR-103/107 levels observed in this mouse model (see Yao et al. study above) could contribute to increase BACE1 remains to be determined. Thus, among at least five miRNAs shown to target BACE1 *in vitro*, that is, miR-29, miR-9, miR-107, miR-298, and miR-328, no clear evidence can be drawn from these mouse models with regard to the physiological or pathological regulation of BACE1 by miRNAs *in vivo*.

While the abovementioned results are interesting, the overall contribution of miRNAs in BACE1 and APP expression regulation remains unclear. The use of gene knockout mice will be indispensible to make definitive conclusions with regard to the role of miRNAs or miRNA gene families in BACE1, APP, and other AD-related gene expression regulation. More transient approaches, for instance using miRNA mimics or inhibitors, will be necessary to address the cause-consequence relationship between miRNA dysregulation and AD progression in the brain. Thus, both classical genetics and miRNA functional tools will be necessary to fully investigate the role of miRNAs in AD mouse models.

5. miRNAs as Potential Diagnostic Tools in AD

Much advancements have been made in the cancer field, for instance, with regard to miRNAs as potential diagnostic tools, some of which are currently available in the clinic. The interest in miRNAs in this field comes from the fact that they are readably detected in human body fluids, making them attractive biological markers. In addition, miRNAs are in general quite stable when compared to protein and/or other RNAs, providing reliable markers of cell or tissue state. While a few groups have explored the role of miRNAs in blood and CSF [32, 33], most AD-based studies have focused mainly on soluble Aβ (and its derivatives) and tau [72, 73]. In the future, it will be interesting to combine and/or compare these species with circulating miRNAs, which can be found in body fluids including exosomes [74]. It is noteworthy that groups have already shown this applicability in mouse models for the Duchenne muscular dystrophy and liver injury [75, 76].

6. Conclusions and Future Perspectives

As summarized above, most studies addressing the role of miRNAs in AD pathology remain correlative in nature, and little or no definitive proof with regard to miRNA target gene regulation *in vivo* is currently unavailable. Addressing these issues is crucial in order to advance our knowledge of the contribution of miRNAs, if any, in AD neuropathology. Because mice are genetically homogenous in nature when compared to humans, they provide unique tools to study miRNA-regulated gene pathways in AD development. Human profiling studies clearly indicate that miRNA expression profiles are altered in AD brain. Whether these changes are specific to AD or reflect an overall loss (or gain) of miRNA function in neurodegenerative disease remains to be determined using adequate comparative analyses. The current profiling data from AD mice suggest that miRNA changes equally occur in disease models, yet some discrepancies still exist. Given our current state of knowledge, the role of miRNAs in AD development, and their applicability as diagnostic and perhaps therapeutic tools into clinic, will require extensive follow-up studies in both *in vitro* and animal models. Specific miRNA gene knockout and/or transgenic mouse is required to address these and other fascinating questions.

Abbreviations

BACE1: Beta-site APP cleaving enzyme
FAD: Familial Alzheimer's disease
Tg: Transgenic 3′UTR
CSF: Cerebrospinal fluid
3′UTR: 3′ untranslated region.

Conflict Interests

The authors declare no conflict of interests.

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