Understanding the role of miR-33 in brain lipid metabolism: implications for Alzheimer's disease

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MAIN TEXT

Because of its incidence and devastating consequences, Alzheimer's disease (AD) has attracted much research attention overthe last decades. Intensive work led to the identification of several cellular and molecular pathophysiologicalprocesses present in the disease, including Tau alterations, β-amyloid (Aβ) deposition, lipid homeostasis dysregulation, excitotoxicity, neuroinflammation,andautophagy defects (Di Paolo and Kim, 2011; Ittner and Gotz, 2011; Heppner et al., 2015; Menzies et al., 2015; Wang and Mandelkow, 2015). Despite much effort, how these different pathways interact and contribute to disease pathogenesis remains poorly understood.

Recent work has begun to investigate a possible role of microRNAs (miRNAs) in the development of AD(Femminella et al., 2015). miRNAsare a class of short non-coding regulatory RNAs that silence gene expression in plants, invertebrates, mammals and humans(Bartel, 2009).Mechanistically, miRNAs bind to short sequences found in target transcripts, resulting in mRNA destabilization and/or translational repression. The target sequence for a particular miRNA could be present in hundreds of mRNAs and a single transcript can, in turn, be targeted by multiple mRNAs(Huntzinger and Izaurralde, 2011). Because of this combinatorial mode of action, miRNAs are thought to act as high-order regulators of gene expression. Not surprisingly, miRNAsare involved in multiple biological processes (van Rooij et al., 2007; Pauli et al., 2011; Tan et al., 2013) andaccumulatingdata suggest that disruptionof miRNAs networks contribute to human diseases including neurodegenerative diseases(Esteller, 2011; Gascon and Gao, 2012; Abe and Bonini, 2013). Moreover, transcriptomic studies havedescribed specific and consistent alterations in miRNAsassociated with AD, and some targets of these miRNAshave beenimplicated in pathophysiological cascadesrelevant to the disease(Femminella et al., 2015). Unfortunately, direct experimental data arguing for a causal role of miRNAs in AD are still scarce.

Work by Horie et al. (2010, 2012) suggests that miR-33 might be particularly important in these pathological cascades. They reported that miR-33 controls the expression of the cholesterol transporter, ABCA1, and reduces HDL cholesterol levels systemically (Horie et al., 2010), andgenetic deletion of miR-33 induced plaque regression in a mouse model of atherosclerosis, (Horie et al., 2012).This is relevant to AD because an extensive literature supports a connection between cholesterol and β-amyloid homeostasis (Puglielli et al., 2001; Jiang et al., 2008; Choi et al., 2015).The presence of Aβ plaques, formed by the sequential cleavage of the amyloid precursor protein (APP) and deposition of Aβ oligomers, is a prominent neuropathologic feature of the disease and is thought to be central to AD development (Nhan et al., 2015).Moreover, polymorphisms of several genes encoding proteins that regulate cholesterol metabolism such as ApoE and ABCA1 have been associated with AD risk (Corder et al., 1993; Koldamova et al., 2010; Cramer et al., 2012).Therefore, if miR-33 also controls ABCA1 expression in the brain, it may have profound effects on cholesterol transport and therefore in Aβ accumulation.

To test this idea, Kim el al. (2015) first examined miR-33 expression across different tissues and cell types. Remarkably, miR-33 was enriched in the brain - particularly in the cortex - and preferentially expressed by neurons. They next asked whether ABCA1 is a target of miR-33 in the brain. For that purpose, the authors quantified cortical levels of ABCA1 in miR-33$^{-/-}$ mice (Horie et al., 2010). Levelswere significantlyhigher in miR-33-deficient animals than inwild-type, suggesting that ABCA1 is also a miR-33 target in the nervous system. miR-33 overexpression in a neuronal cell line as well as in primary astrocytes also regulated ABCA1 levels, further confirming the direct regulation of ABCA1 via miR-33.

The authors next asked whether miR-33 affected Aß production. Indeed, in cell lines expressing mutated APP, miR-33 transfection resulted not only in a reduction of ABCA1 but also in increased secretion of Aβ. The ability of different cell types to degrade synthetic Aβ was also impaired by miR-33. Remarkably, restoring ABCA1 levels (using a miR-33-resistant construct) abolished the effects of miR-33 onAβ

homeostasis. Taken together, these findings strongly suggested that miR-33 control Aβ deposition by modulating ABCA1 levels.

Finally, Kim el al. (2015) validated the involvement of miR-33 in Aβ □ □ □ □ □ □ □ □ *in □ vivo*□ First, they showed that miR-33$^{-/-}$ mice had reduced cortical levels of Aβ products (Aβ$_{40}$ and Aβ$_{42}$) but normal APP levels. Then, using a mouse model of AD, they found that chronic treatment with a miR-33 antagonist caused a significant decrease in Aβ$_{40}$. Overall, the data presented by Kim et al.(2015) provided additional evidence of the links between cholesterol and Aβ metabolism in the brain and, more importantly, pinpointed the essential role of miR-33 in modulating this pathogenic pathway.

Kim el al. (2015) demonstrated that most cellular changes induced by manipulation of miR-33 levelscould be rescued by ABCA1, indicating that this transporter is a central target in miR-33 regulatory events. Consistent with this notion, many previous studies haveshowed that sometargets are more important than others depending on the context (Cassidy et al., 2013; Gascon et al., 2014). Nevertheless,miRNAs simultaneously silence multiple transcripts and regulation of other targets might result in synergistic effects.In this regard, it is worth noting that miR-33 controls the expression of SREBF1,a transcription factor known to modulateseveral genes involved in the synthesis and uptake of cholesterol(Horie et al., 2013). Furthermore, miR-33 isembedded in the locus of SREBF2, another member of the same family(Horie et al., 2010). Since intragenic miRNAs frequently target their host genes (Kos et al., 2012; Yuva-Aydemir et al., 2015), an attractive hypothesis is that miR-33 might controllipid homeostasis at multiple levels acting thereby as a molecular hub (Fig. 1).

Along the same lines, computational algorithms (e.g. TargetScan) indicate that miR-33 may target multiple kinases families including those involved in Tau phosphorylation such as cyclin-dependent kinases or mitogen-activated protein kinases (Rudrabhatla, 2014).It is important to remember that although multiple theoretical scenarios regarding AD pathogenesis have been postulated, no single

theory can successfully account for the clinical heterogeneity observed in the disease. Kim et al. (2015)demonstrated in vitro and in vivo a connection between Aβ deposition, cholesterol homeostasis and miR-33 in the brain suggesting that multiple mechanisms may simultaneously contribute to disease. It would be therefore interesting to assess, for example,whether miR-33 affects other known cascades such as tau phosphorylation (Fig. 1).

It is important to note that Kim el al.(Kim et al., 2015)did not investigate miR-33 levels in the brain of AD patients. A rapid survey to the deposited data in GeoR profiles showed that no changes in either miR-33a or miR-33b (two miR-33 homologs found in humans) were observed in three independent studies (Hebert et al., 2013; Lau et al., 2013; Santa-Maria et al., 2015). Although these data do not support the hypothesis that miR-33 contributes to AD pathology, they should be interpreted cautiously given the number of confounding variables intrinsic to these profiling studies. In addition to the heterogeneity of AD itself, variable comorbidities in analyzed cohorts, different post-mortem intervals, or technicaldisparities might preclude the detection of miRNAs changes. In this regard, one could take advantage of miRNA profiling in mouse models of AD. Here, again, miR-33 expression was not significantly modified in the hippocampus of two different transgenic mice overexpressing APP (Barak et al., 2013; Noh et al., 2014) suggesting that miR-33 might not be involved in the pathogenesis of the disease. Nonetheless, as Kim el al. (2015) stated in the discussion, miR-33 may represent an attractive therapeutic target.

Regarding the therapeutic potential of miR-33 in AD, one should first address an essential question: would altering miR-33 levels alleviatecognitivedeficits associated with AD? This is an important questionthat remains unexplored. Notably, there is conflicting evidence regarding the contribution of Aβ burden on functional impairment: some treatments have been shown to improve behavioral deficits withoutaffecting Aβ pathology (Jankowsky et al., 2005; Cuadrado-Tejedor et al., 2011) whereas others found an inverse correlation between plaque content and behavioral performance (Cramer et al., 2012; Verma et al., 2015). Nevertheless,

accumulating data indicate that soluble Aβ, rather than the insoluble material in the plaques, is the toxic species in AD(Fedele et al., 2015; Ferreira et al., 2015). Since miR-33 modulates both the generation and removal of Aβ oligomers, results obtained in this study support apositive effect of manipulating miR-33levelson behavioral outcomes. Further work should evaluate this crucial issue and clarify whether treatments targeting miR-33 in mice are beneficial to revert memory loss or other AD-associated symptoms as well as molecular pathology.

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FIGURE LEGENDS

Figure 1. Schematic representation of the main findings reported in this study as well as of other pathways potentially regulated by miR-33 relevant to AD. Kim et al. (2015) demonstrated the essential function of miR-33 in modulating ABCA1 expression and how this transporter influenced cholesterol content of ApoE and, thereby, Aβ production and degradation (black fonts, center). miR-33 might exert further control on lipid metabolism by regulating the expression of the transcription factors SRBEF1 and 2 (white fonts, left). Other miR-33 targets (e.g. cyclin-dependent kinases) might further contribute to AD pathogenesis by activating complementary pathways (e.g. Tau phosphorylation, (white fonts, right)).