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The path to microRNA therapeutics in psychiatric and neurodegenerative disorders

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INTRODUCTION

The multi-functional role of RNA as a molecular regulator spans a broad range of classifications as protein-coding and non-protein coding RNA transcripts. Notably, the microRNA (miRNA) class of non-coding RNAs have been implicated in a vast majority of the established signaling cascades (Bartel, 2009). Brain-localized miRNAs are of particular interest for neurological diseases which have a complex etiology and no currently effective therapeutic options. The transcriptomic targets of an miRNA can encompass numerous cellular pathways, consistent with the extensive molecular disruption linked to neurological disease onset. In this review, we discuss how various model systems can be integrated into the translation of miRNAs as novel clinical targets.

CONSERVED ROLE OF NEURONAL miRNAs

The conserved role of miRNAs in neuronal functions underscores their relevance in the molecular dynamics between normal and pathogenic mechanisms. Indeed, Drosophila, rodents, monkeys, and humans have all shown significant sensitivity to microRNA modulation (Jin et al., 2004; Ashraf et al., 2006; Elmen et al., 2008; Hollander et al., 2010). Notably, some core components of the miRNA processing machinery, guided by the RNA-induced silencing complex (RISC), are shared between lower vertebrates and primates, such as the Argonaute-interacting proteins, GW182 silencing complex (RISC), are shared between lower vertebrates and primates, such as the Argonaute-interacting proteins, GW182 silencing complex (RISC), and the miRNA processing machinery itself, such as Drosha and Dicer, are all subject to disruption with neurologically relevant disease. Here, we review how a diverse range of biological systems, including Drosophila, rodents, and primates such as monkeys and humans, can be integrated into the translation of miRNAs as novel clinical targets.

miRNA REGULATION IN NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISORDERS

Several of the more extensively reported brain-enriched miRNAs, such as miR-9, miR-34, miR-124, miR-128, miR132, miR-219, have predominantly identical mature sequences across species, including humans, monkeys, mice, and Drosophila (Kapsimali et al., 2007; Hu et al., 2011; Juhila et al., 2011). The conservation of those miRNAs spans from the 5′ seed region to the 3′ end of the transcript. Moreover, the precursor sequence for some of the brain-enriched miRNAs, including miR-9 and miR-124, are also identical between humans and mice, further supporting a highly conserved function for those transcripts.

The microRNA (miRNA) class of non-coding RNAs exhibit a diverse range of regulatory roles in neuronal functions that are conserved from lower vertebrates to primates. Disruption of miRNA expression has compellingly been linked to pathogenesis in neuropsychiatric and neurodegenerative disorders, such as schizophrenia, Alzheimer’s disease, and autism. The list of transcript targets governed by a single miRNA provide a molecular paradigm applicable for therapeutic intervention. Indeed, reports have shown that specific manipulation of a miRNA in cell or animal models can significantly alter phenotypes linked with neurological disease. Here, we review how a diverse range of biological systems, including Drosophila, rodents, and primates such as monkeys and humans, can be integrated into the translation of miRNAs as novel clinical targets.
altered miRNA profiles have been identified, and a summary of the
dysregulated miRNAs and the biological source they were profiled
from are outlined in Table 1 (Jin et al., 2004; Abu-Elneel et al.,
2008; Li et al., 2008; Pietrzynowski et al., 2008; Hunsberger et al.,
2009; Yang et al., 2009; Zhou et al., 2009; Zhu et al., 2009; Beveridge
et al., 2010; Hollander et al., 2010; Im et al., 2010; Sarachana et al.,
2010; Saus et al., 2010; Xu et al., 2010a,b; Baudry et al., 2011a,b;
Eipper-Mains et al., 2011; Ghahramani Seno et al., 2011; Haramati
et al., 2011; Mouillet-Richard et al., 2011; O’Connor et al., 2011;
Shaltiel et al., 2012). In schizophrenia, miRNA profiling has now
been completed in several patient populations, primarily focused
within the cortex (Perkins et al., 2007; Beveridge et al., 2010; Kim
et al., 2010; Moreau et al., 2011; Santarelli et al., 2011). Although
a majority of the miRNA profiling studies for neurological dis-
ease have been performed from brain, miRNA dysregulation has
also been observed in other sources such as cerebral spinal fluid
(CSF), plasma, serum, and peripheral blood (Schipper et al., 2007;
Cogswell et al., 2008; Gardiner et al., 2011; Ghidoni et al., 2011;
Lai et al., 2011). Beveridge and Cairns (2011) recently reviewed the
various studies to compare and contrast the collection of miRNA
results in schizophrenia. Interestingly, a few of the miRNA fami-
lies, including the miR-15 and miR-30 families, have consistently
shown disruption in several of the population analyses (Beveridge
and Cairns, 2011). We examined the bioinformatic mRNA tar-
gets of miR-15 and miR-30 with Targetscan and found several
mRNAs which are strongly linked with schizophrenia, includ-
ing neuregulin and synaptotagmin (Kim et al., 2007; Kao et al.,
2010).

Psychiatric symptoms can also co-exist in patients with neu-
rodegenerative pathology, such as Huntington’s disease (HD),
Frontotemporal dementia (FTD), Alzheimer’s disease (AD),
Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS),

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated miRNAs</th>
<th>Biological profiling source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>106b, 107, 128a, 134, 150, 15a, 15b, 16, 17, 181a, 181b, 195, 199a*, 19a, 20a, 20b, 212, 219, 24, 25, 26b, 27a, 29a, 29b, 30a-5p, 30b, 30d, 328, 346, 382, 487a, 9-3p, 92, let-7d, let-7e, 652, 7</td>
<td>Human cortex (temporal and prefrontal)</td>
<td>Beveridge et al. (2008, 2010), Zhu et al. (2009), Perkins et al. (2007), Santarelli et al. (2011)</td>
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<td></td>
<td></td>
<td>Cortex from mouse model of schizophrenia</td>
<td>Kocerha et al. (2009)</td>
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<td></td>
<td></td>
<td>Human genomic DNA</td>
<td>Ripke et al. (2011), Xu et al. (2010a)</td>
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<tr>
<td></td>
<td></td>
<td>Human blood</td>
<td>Xu et al. (2010a), Lai et al. (2011)</td>
</tr>
<tr>
<td>Schizophrenia or bipolar disorder</td>
<td>106b, 132*, 132, 133b, 138, 140-3p, 145*, 145, 148b, 190, 20a, 20b, 27a, 301a, 324-5p, 335, 376a*, 489, 494, 497, 660</td>
<td>Human cortex</td>
<td>Moreau et al. (2011), Kim et al. (2010)</td>
</tr>
<tr>
<td>Autism</td>
<td>106a, 106b, 128, 129, 132, 140, 146b, 148b, 15a, 15b, 181d, 193b, 21, 212, 23a, 27a, 320a, 381, 431, 432, 484, 539, 550, 598, 652, 7, 93, 95</td>
<td>Human cerebellum</td>
<td>Abu-Elneel et al. (2008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoblastoid cell lines</td>
<td>Sarachana et al. (2010), Ghahramani Seno et al. (2011)</td>
</tr>
<tr>
<td>Depression</td>
<td>16</td>
<td>Mouse serotonergic raphe nuclei</td>
<td>Baudry et al. (2011a,b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Human genomic DNA (blood)</td>
<td>Saus et al. (2010), Xu et al. (2010b)</td>
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<tr>
<td></td>
<td></td>
<td>Human prefrontal cortex</td>
<td>Smallheiser et al. (2012)</td>
</tr>
<tr>
<td>Addiction</td>
<td>212, 132, 124, 77-7d, 181a</td>
<td>Brain tissue from rat cocaine addiction model</td>
<td>Hollander et al. (2010), Chandrasekar and Dreyer (2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain tissue from mouse cocaine addiction model</td>
<td>Eipper-Mains et al. (2011)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>132, 34</td>
<td>Striatal neuronal cultures for model of alcohol exposure</td>
<td>Pietrzynowski et al. (2008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain tissue from mouse model of anxiety</td>
<td>Shaltiel et al. (2012), Haramati et al. (2011)</td>
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</tbody>
</table>
A selection of cell and animal models have been engaged in the AD (Cogswell et al., 2008), and progressive supranuclear palsy clinical trials. Our group examined the regulation of miRNAs the progression toward testing of miRNA-based therapeutics in to uncover a role for miR-7 in PD pathology (Junn et al., 2009). In tetrahydropyridine; MPTP) for Parkinson’s disease (PD) was used a neurotoxin induced mouse model (1-methyl-4-phenyl-1,2,3,6-

in vivo knock-out and knock-in mice have also been valuable platforms that have effectively been utilized for neurons, and induced pluripotent stem (iPS) cells are a few of the preliminary search for miRNAs with clinical relevance for neu-

depth molecular analysis of functional miRNAs (Vo et al., 2005; Cole et al., 2008; Agostini et al., 2011; Arias-Carrion and Salama, 2011; Kim et al., 2011; Saba et al., 2012). Indeed, cell-based sys-

tems have led to successful large-scale screening studies as well as in-depth molecular analysis of functional miRNAs (Vo et al., 2005; Cole et al., 2008; Connelly et al., 2012). For example, the discovery that neuronally enriched miR-132 is regulated by cAMP-response element binding protein (CREB) was initiated through a genome-wide screen in rat PC12 neuronal cells (Vo et al., 2005). Not all miRNAs will have a functional biological role, however, cell-based screens can facilitate the identification of promising candidates.

In parallel with the in vitro findings, studies in non-primate animal models have significantly expanded our understanding of miRNA biology in psychiatric and neurodegenerative disorders (Kocerha et al., 2009; Hollander et al., 2010; Lee et al., 2011; Li et al., 2011). Animal studies are a critical step in the progression toward testing of miRNA-based therapeutics in clinical trials. Our group examined the regulation of miRNAs in mice with pharmacological induction of a schizophrenia-associated behavioral phenotype (Kocerha et al., 2009). Likewise, a neurotoxin induced mouse model (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP) for Parkinson’s disease (PD) was used to uncover a role for miR-7 in PD pathology (Junn et al., 2009). In addition to pharmacologically treated animal models, transgenic, knock-out and knock-in mice have also been valuable in vivo resources (Lee et al., 2011; Tao et al., 2011). Indeed, transgenic expression of the AD-causative amyloid precursor protein (APP) gene in mice provoked significant disruption in neuronal miRNA expression (Schonrock et al., 2010).

In addition to mice, rats as well as zebrafish and other vertebrate species have been integral in the study of neuronal miRNA pathways prior to testing in primate models (Yang et al., 2011; Tal et al., 2012). Indeed, recent reports identified miRNAs in zebrafish directly linked to neurobehavioral responses and neuronal differentiation (Tal et al., 2012). The exploration of miRNAs which regulate central nervous system functions, however, is not limited to vertebrate species. Drosophila, an invertebrate model, have been widely used for many years to examine or further define molecular mechanisms. Moreover, studies in Drosophila recently revealed that the conserved miRNA miR-34 mediates aging and neurodegenerative processes (Liu et al., 2012a), further substantiating that all biological models are applicable in the investigation of non-coding RNAs. Additionally, as each miRNA may regulate a number of transcripts and therefore off-target effects may result when altered, animal and cell models may help to filter out those candidates.

PRIMATE MODELS AND miRNA PRE-CLINICAL EVALUATION

Arguably, a principal goal in the field of non-coding RNAs, including miRNAs, is to uncover transcripts which can ultimately lead to advancements in human health. Correspondingly, there are numerous studies which have profiled miRNA expression from humans with and without a disease diagnosis. Although some of those reports have focused on peripheral tissues, a subset of those analyses have specifically examined miRNA transcripts in distinct brain regions (Hebert et al., 2008; Kocerha et al., 2011; Santarelli et al., 2011). Genome-wide association (GWAS) studies and microarray profiling have both been used to identify miRNAs which are potential disease risk factors for neurodegenerative and psychiatric disorders (Rademakers et al., 2008; Hollander et al., 2010; Kocerha et al., 2011; Richardson et al., 2011; Ripke et al., 2011). Furthermore, there can be disruption of a cluster or multiple members within an miRNA family, such as with miR-29. In brain tissue from a cohort of Alzheimer’s patients, miR-29a and miR-29b expression were both significantly repressed in patients with increased levels of beta-secretase BACE1 (Hebert et al., 2008). BACE1 is a direct mRNA target for the miR-29 family and has consistently been linked to AD pathology. Therefore, correlation of expression for a miRNA and its targets in the transcriptome, as well as identification of disruption in miRNA families, can all contribute to effective discovery of new treatment alternatives for diagnosed patients.

The brain structure and related functions of humans and monkeys are strikingly similar (King and Wilson, 1975; McConkey and Varki, 2000; Paabo, 2001; Perkins et al., 2010; de Araujo et al., 2012), suggesting that monkeys are a relevant primate model for pre-clinical investigation of miRNAs in neurological dysfunction. Notably, certain key cell types in the brain linked to disease pathology, such as mirror neuron disruption in autism (Perkins et al., 2010), are primarily specific to primate physiology. Moreover, there is extensive conservation in miRNAs between primates, including those which are localized in the central nervous system.
Table 2 | miRNAs associated with neurodegenerative disease.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated miRNAs</th>
<th>Biological profiling source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal dementia (FTLD)</td>
<td>922, 516a-3p, 571, 548b-5p, 548c-5p</td>
<td>Human cortex and cerebellum</td>
<td>Kocerha et al. (2011)</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>137, 181c, 9, 29a, 29b, 34a, 181b</td>
<td>Human blood</td>
<td>Geekiyanage et al. (2011) , Schipper et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>137, 181c, 9, 29a, 29b</td>
<td>Human serum</td>
<td>Geekiyanage et al. (2011)</td>
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<tr>
<td></td>
<td>101, 106b, 107, 125b, 137, 142-3p, 142-5p, 145, 151-5p, 15a, 181c, 184, 185, 194, 197, 19b, 210, 212, 214, 219-2-3p, 22, 223, 26b, 27b, 29b, 29a, 29a/b-1, 29b-1, 300, 30a1, 320, 326, 330-5p, 338-3p, 338-5p, 361-3p, 363, 382, 424, 425, 509-5p, 511, 516a-5p, 516b, 525-5p, 551b, 576-5p, 583, 9, 93, 98, let-7e, let-7f, let-7i 9, 125b, 128, 124a 105, 10a, 10b, 125a, 126*, 126, 127, 135a, 138, 141, 142-5p, 143, 146b, 151, 154, 15b, 181a, 181c, 186, 191, 194, 195, 197, 199a*, 204, 205, 214, 216, 221, 302b, 30a-3p, 30a-5p, 30b, 30c, 30d, 32, 338, 345, 362, 371, 374, 375, 380-3p, 422b, 429, 448, 449, 451, 455, 494, 497 501, 517a, 517b, 518b, 518f, 520a*, 526a, 7f, 99a 125b, 106b, 107, 124, 132, 145, 146b, 148a, 17-5p, 200c, 20a, 210, 212, 26a, 27a, 27b, 30c, 30e-5p, 34a, 381, 422a, 423, 425, 9, 92, let-7b, 100 106a, 106b, 125b, 137, 146a, 147, 148b, 153, 17, 17-5p, 181c, 187, 20a, 20b, 21, 212, 26a, 27a, 29a, 29b, 301, 30b, 30c, 30e-5p, 323-3p, 328, 34a, 361, 365, 376b, 381, 409, 422a, 423, 433, 520c, 644, 655, 664, 700, 7g, 7i 9, 92 34a, 103, 107, 146a, 106b, 16, 34c, 20a, 17-5p 214, 23a, 23b, 486-3p, 30e*, 143, 128, 27a, 27b, 324-5p, 422a</td>
<td>Human hippocampus Human CSF Human brain Cell cultures AD mice models Bioinformatic single nucleotide polymorphism (SNP) analysis</td>
<td>Lukiw (2007) Cogswell et al. (2008) Cogswell et al. (2008), Hebert et al. (2009), Smith et al. (2011), Wang et al. (2008) Long and Lahiri. (2011), Kim et al. (2011), Boissonneault et al. (2009), Patel et al. (2008), Schonrock et al. (2010), Delay et al. (2011), Hebert et al. (2009), Smith et al. (2011) Yao et al. (2010), Li et al. (2011), Wang et al. (2009, 2010), Liu et al. (2012b), Zovoilis et al. (2011), Hebert et al. (2009) Mallick and Ghosh. (2011)</td>
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</table>
Viral and antisense-mediated targeting of non-coding transcripts

As discussed above, a considerable number of the 413 miRNAs expressed in human brain, 366 of those transcripts are also detectable in rhesus macaque brain (Hu et al., 2011). Correspondingly, a number of those miRNAs are also detectable in mouse cortex and hippocampus by microarray and sequencing efforts, such as miR-9, miR-124, miR-128, and miR-132 (Juhila et al., 2011), suggesting that mouse models can be effective prior to testing in primates.

There have been considerable technological advancements in recent years with primate focused research, including with non-coding RNA biology. Groups have successfully delivered modified-antisense oligonucleotides (ASO) into monkeys to inhibit the function of specific miRNAs with minimal off-target effects (Elmen et al., 2008; Petri et al., 2009; Lanford et al., 2010). To date, the ability to modulate miRNAs in primates is restricted to peripheral administration, however, delivery of potential therapeutics across the blood brain barrier could be a future attainable milestone. Progress has also been made in other capacities with primates, including with the generation of transgenic monkeys. Our group established the first transgenic rhesus macaques in 2001 (Chan et al., 2001), which subsequently led to the development of a cohort for HD transgenic monkeys (Yang et al., 2008), a resource directly applicable to assess miRNA functions in a primate model of neurodegenerative disease. Moreover, from the HD monkeys we derived iPSCs which display a progressive cellular phenotype (Chan et al., 2010), providing an in vitro platform to complement the in vivo analyses for therapeutic and biomarker discovery, including non-coding RNA targets.

In primates, the progression of neurodegeneration and psychiatric deficits is typically gradual, developing over years, rather than weeks or months. Correspondingly, longitudinal analyses of molecular and neurobehavioral changes are fundamental to the monitoring and subsequent discovery of new treatments (Insel, 2009; Thompson et al., 2011). Indeed, longitudinal studies are readily implementable in primate species such as monkeys and humans, including collection of peripheral blood samples for molecular analysis throughout disease progression and parallel correlation with brain morphology by magnetic resonance imaging (MRI; Thompson et al., 2011; Waber et al., 2012; Zhang et al., 2012). The correlation of miRNA expression with disease trajectories may help identify functional non-coding RNA transcripts involved in neuronal pathogenesis.

**APPROACHES FOR miRNA MODULATION AND CLINICAL TRANSLATION**

As discussed above, a considerable number of in vitro and in vivo models are increasingly becoming available for miRNA functional studies. In conjunction, there have been also significant advances in the approaches to modulate or detect specific miRNAs. Viral and antisense-mediated targeting of non-coding transcripts are routinely applied to alter expression levels, however, technical improvements have allowed for increased effectiveness and efficacy. For example, locked nucleic-modified antisense oligonucleotides (LNA-ASO) significantly enhance the specificity and stability of miRNA silencing (Elmen et al., 2008; Stenvang et al., 2008; Kocerha et al., 2009; Hollander et al., 2010; Obad et al., 2011).

Notably, the LNA-ASO can be administered in vivo to animal models through different routes, such as intracerebroventricular (icv) delivery to penetrate multiple brain regions (Kocerha et al., 2009; He et al., 2010), or local stereotactic injections for site-specific miRNA silencing (Gao et al., 2010; Hollander et al., 2010). LNA-modified probes also intensify the detectability of non-coding RNAs for in situ localization (Havelda, 2010), which facilitates examination of less abundant transcripts. There are other chemical modifications available for ASO, such as 2′-O-methyl RNA, 2′-O-methylloxethyl RNA, and phosphorothioate RNA (Ruberti et al., 2011), some of which have also been successfully utilized in the context of in vivo silencing (Cheng et al., 2009).

In addition to viral and antisense methods, nanoparticle delivery of neurogenic miRNAs provide a means for brain distribution of selected transcripts. Just recently, reports showed that rabies virus glycoprotein (RGV)-labeled nanomaterials resulted in specific delivery of miR-124 to neuronal cells (Hwang do et al., 2011). Nanotechnology has also been employed to silence miRNA function, such as with miR-122 conjugated to gold nanoparticles in myeloma cells (Crew et al., 2012), suggesting this technology is effective in the repression or stimulation of miRNA expression.

Importantly, silencing of miRNAs in animal embryos have also provided significant insight to their role in brain development. Recent reports have shown that injection of morpholinos to block miR-9 activity in the embryos of Xenopus tropicalis (Bonev et al., 2011) or zebrafish (Tal et al., 2012) substantially altered neuronal functions in the developing animals. Furthermore, overexpression or silencing of miR-9 via electroporation in mouse embryos revealed that Cajal Retzius neuronal cell differentiation is regulated through Forkhead box protein G1 (FOXG1; Shibata et al., 2008). Collectively, these reports indicate that miRNA activity can be modulated in vivo at various developmental stages to assess their implications in brain functions.

Overall, the technical developments in miRNA biology mentioned above facilitate the translation of select miRNA transcripts for future clinical intervention. Indeed, there are human trials currently being conducted to assess miRNA-modulation in disease pathogenesis, including the use of LNA-ASO (Seto, 2010; Montgomery and van Rooij, 2011). To date, the reported human trials have focused on miRNA regulation in peripheral organs, however, therapeutic targeting of the brain remains a future objective. Polymer (Cheng and Saltzman, 2012), lipid (Shi et al., 2012), and polylysine (Jin et al., 2012) based nanoparticle modulation of miRNAs has also been reported. Although a majority of the nanodelivery methods for miRNA studies have focused on non-neuronal cells, there is great potential for their application to the central nervous system.

**CONCLUSION**

The discovery and development of miRNA-based therapeutics, as well as the diverse range of molecular cascades they can regulate, offer a new approach for treating diseases with a heterogeneous or epigenetic origin. There are numerous psychiatric and neurodegenerative diseases with no effective treatments due to their
complex etiology and therefore may be ideally positioned for clinical targeting of pleiotropic miRNAs.

**ACKNOWLEDGMENTS**

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MicroRNAs in neuropsychiatry and neurodegeneration


Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.