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REVIEW

MiR-137: an important player in neural development and neoplastic transformation

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MicroRNAs (miRNAs) represent an important class of small regulatory RNAs that control gene expression posttranscriptionally by targeting mRNAs for degradation or translation inhibition. Early studies have revealed a complex role for miRNAs in major biological processes such as development, differentiation, growth and metabolism. MiR-137 in particular, has been of great interest due to its critical role in brain function and putative involvement in the etiology of both neuropsychiatric disorders and cancer. Several lines of evidence suggest that development, differentiation and maturation of the nervous system is strongly linked to the expression of miR-137 and its regulation of a large number of downstream target genes in various pathways. Dysregulation of this molecule has also been implicated in major mental illnesses through its position in a variant allele highly associated with schizophrenia in the largest mega genome-wide association studies. Interestingly, miR-137 has also been shown to act as a tumor suppressor, with numerous studies finding reduced expression in neoplasia including brain tumor. Restoration of miR-137 expression has also been shown to inhibit cell proliferation, migration and metastasis, and induce cell cycle arrest, differentiation and apoptosis. These properties of miR-137 propose its potential for prognosis, diagnosis and as a therapeutic target for treatment of several human neurological and neoplastic disorders. In this review, we provide details on the discovery, targets, function, regulation and disease involvement of miR-137 with a broad look at recent discovery in this area.

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INTRODUCTION

MicroRNAs (miRNAs) are a large class of non-coding RNAs regulating many biological processes in a wide range of organisms including plants, animal species and virus.[1] These molecules exert their regulatory roles by modulation of gene expression through degradation of mRNA or suppression of protein synthesis.[2] Over the last few years, miRNAs have been the focus of many studies, providing evidence that these small RNAs have a significant role in the modification of numerous biological pathways.[3] It is also evident that any abnormality in miRNA function can cause cellular malfunction, which in turn may lead to a disorder.[4]

MiRNA genes are initially transcribed into a primary RNA transcript (pri-miR) before their stem loop structure undergoes processing in the nucleus to form a ~70 nt long intermediate termed the precursor miRNA (pre-miR). This is performed by the microprocessor complex comprising the RNase III Drosha and a double-stranded RNA-binding protein, DiGeorge syndrome critical region gene 8 (DGCR8).[5,6] Pre-miRs are then transported to the cytoplasm through the nuclear pores by Exportin-5 complex,[7] where further processing occurs by a second RNase III known as Dicer and its associated trans-activation response RNA binding protein (TRBP) to yield double stranded RNAs, 18–24 nt in length.[8–10] These are subsequently unwound and the mature single-stranded miRNA is incorporated into the argonaute protein-containing RNA-induced silencing complex (RISC). In this complex the miRNA functions as a template for homology directed mRNA targeting of the 3′ untranslated region (UTR).[11,12] The intermolecular base pairing occurs primarily at 3′ UTR segments with sequence complementarity to the miRNA 'seed' region consisting of 6 nt from positions 2 to 7 or 8[13] (Figure 1).

MiRNAs are able to posttranscriptionally regulate a large number of genes by either mRNA degradation or translational inhibition.[14] Although some miRNAs are widely expressed others have stage, tissue or cell type-specific expression patterns.[15] MiRNA genes can be exonic, intronic or reside within intergenic transcripts.[16] Significantly, mature miRNA can bind to their target 3′ UTRs despite mismatched pairing, enabling each miRNA to regulate hundreds of mRNA targets.[17] Multiple miRNA can also regulate a single gene,[18,19] such that different miRNAs are able to cooperate in a given pathway and share their regulatory responsibilities.

Bioinformatic studies estimate that miRNA regulate expression of up to 80% of genes in human[20] encompassing a wide range of cellular functions such as development,[21] cell proliferation,[22] differentiation,[23] apoptosis,[24] signal transduction[25] and cell cycle.[26] MiR-137 is one of several miRNAs that have a significant role in cellular biology, localizing on human chromosome 1p22 within the gene for the non-protein-coding RNA AK094607.[27] MiR-137 has a critical regulatory role in brain function, with several reports displaying an association with proliferation and differentiation during development.[28] The miR-137 host gene is strongly associated with the etiology of many psychiatric disorders including schizophrenia (SZ)[29] and bipolar disorder (BD).[30] Dysfunction of miR-137 has also been shown to contribute to several human cancer types such as neuroblastoma[31] and glioblastoma multiforme.[32]

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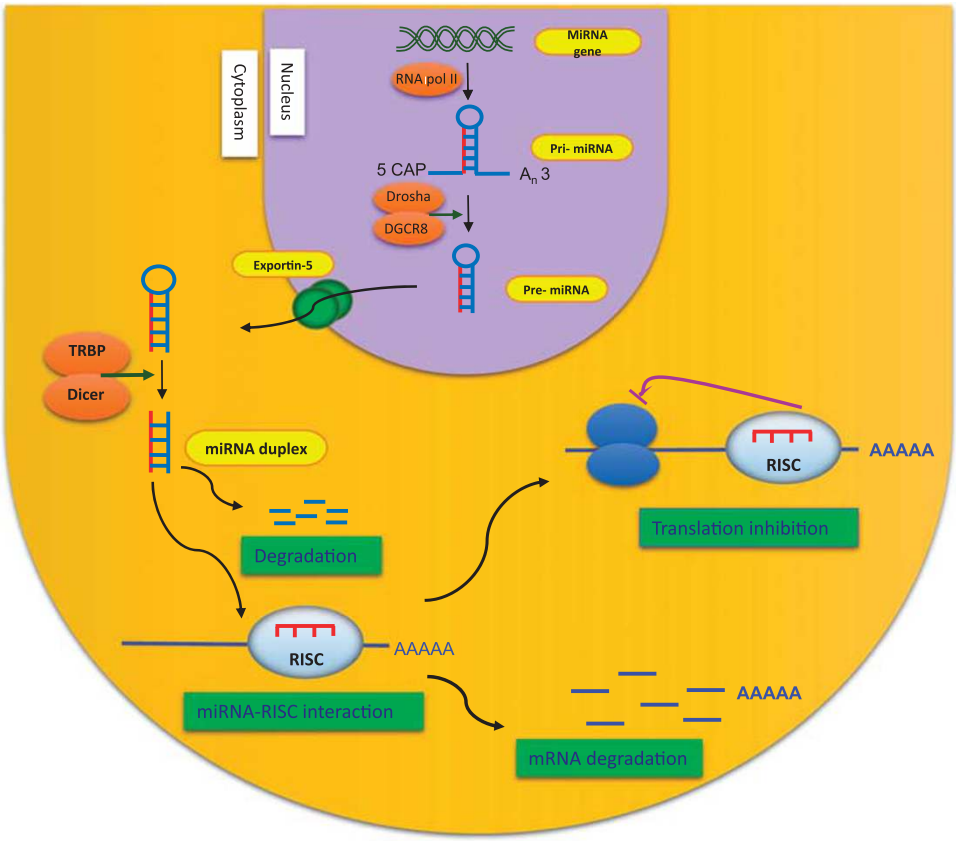

Figure 1. Schematic of miRNA biogenesis pathway and function. MicroRNA (miRNA) is initially transcribed by RNA pol II transcription factor and form a hairpin structure termed pri-miRs. Then Drosha and DGCR8 complex cleave the molecule producing pre-miRs in the nucleus. Exportin-5 transfers the double strand miRNA into the cytoplasm where miRNA undergo further editing by TRBP and Dicer complex to form miRNA duplex, which are eventually unwound to reveal the mature miRNA. MiRNA interact within a RISC complex and provide guidance for targeting mRNAs for degradation or translational repression.

In this review, we summarize our current understanding of miR-137 in cell biology and its association with human disorders with an eye on the potential use of miR-137 as a prognostic/diagnostic signature and target for therapeutic development.

DISCOVERY AND TARGETS

MiR-137 is a classic 23-nt microRNA located within a long non-coding host gene, *MIR137HG*. This transcriptional unit on chromosome 1 is over 62 kb long and is predicted to produce four splice variants ranging from over 2.5 kb to below 1 kb. There is also a 15-bp variable tandem repeat localized in the primary transcript of miR-137, 5′ to the pre-miR-137, shown to change the posttranscriptional processing of miR-137 through alteration of its secondary structure[27] (Figure 2).

The first report of miR-137 dates back to 2002, where a study aimed to identify functional miRNAs and their tissue-specific expression pattern in mammalians. Lagos-Quintana *et al.*[33] cloned microRNAs from nine different adult mouse tissues including heart, liver, small intestine, colon, cortex, cerebellum and midbrain, with 34 novel miRNAs, including miR-137, being identified specifically in midbrain cortical tissue. Later, another study by Landgraf and colleagues validated this miRNA expression in various human and rodent tissue, along with over 250 other miRNA. This miRNA was also found to be enriched in the nervous system.[34]

Using a bioinformatic approach, over 1000 putative genes have been predicted to be targets of miR-137.[35] Around 5% of these have been experimentally validated (Figure 3); mostly via gene expression profiling, luciferase expression reporter and western blot assay in a wide variety of transfected cell lines. These functional analyses are summarized in Table 1, and highlight target genes involved in a large number of pathways including neural development, cell cycle, differentiation and proliferation.

FUNCTION

A number of studies have demonstrated that microRNA networks are responsible for posttranscriptional modulation of gene expression. They are present in almost all tissue types and mediate a vast range of biological processes (Table 1). MiR-137 is a brain-enriched miRNA in mouse and human[33,36,37] with a high expression in the cortical brain regions, and hippocampus and low expression in cerebellum and brain stem.[37] This is consistent with evidence from several studies suggesting that it regulates cell proliferation and differentiation, in both the embryonic and adult brain (Figure 4). Sun *et al.* demonstrated that miR-137 promoted cell differentiation while inhibiting proliferation of embryonic neuronal stem cell by downregulating the LSD1 gene through a regulatory loop with the transcriptional co-repressor TLX.[28] Work by Tarantino *et al.* established that miR-137 was increased upon differentiation and functional analysis demonstrated that miR-137 could directly target Jarid1b, also known as KDM5b, resulting in differentiation of mouse embryonic stem cells (ESCs).[38] MiR-137 was found to be expressed at the mitotic phase of the cell cycle and highly upregulated during differentiation of ESCs into neural

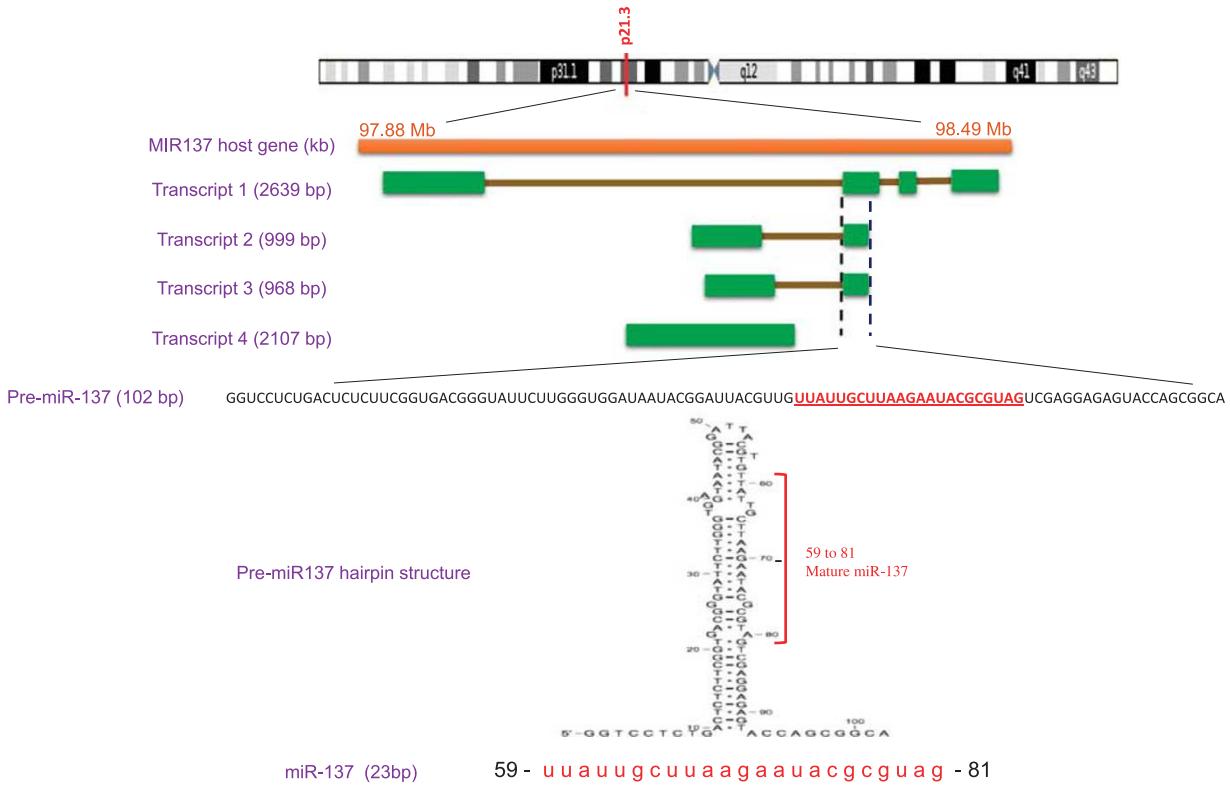

Figure 2. Genomic location, transcripts and sequence of miR-137 in human. The gene is 61 kb long situated in short arm of chromosome 1 producing four transcripts. The pri-miR is 102 nt in length which is cleaved to a 23-nt mature miRNA (miR-137).

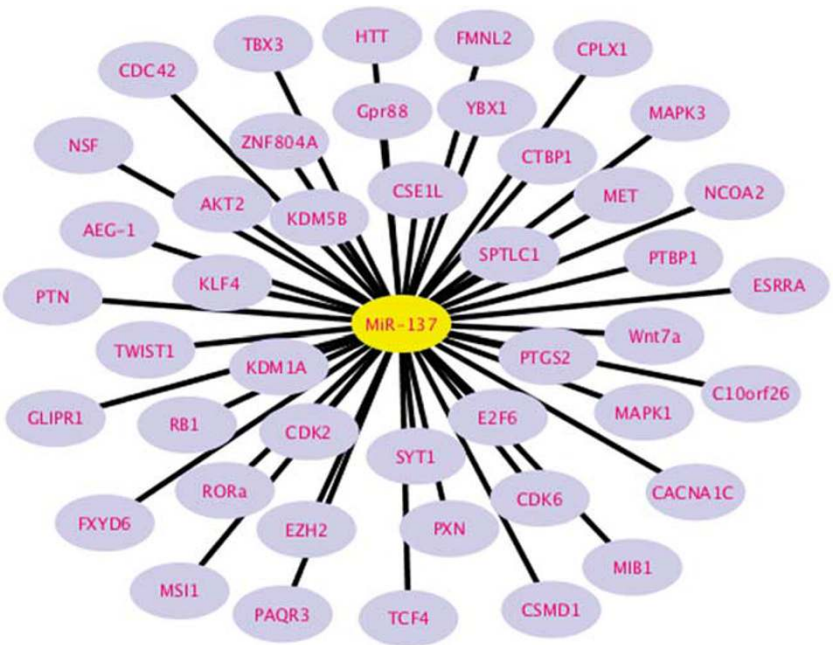

Figure 3. Experimentally validated target genes of miR-137. Approximately 50 genes have been identified to be directly regulated by miR-137 and most confirmed by luciferase assay and western blot. The target genes of miR-137 are involved in different biological pathways mainly cell cycle, proliferation and differentiation.

cells.[39] This upregulation led to repression of two ES cell transcription factors, Klf4 and Tbx3, which were directly targeted by miR-137 (Figure 4a). Similar findings were obtained from a study showing that miR-137 promoted neural differentiation of various stem cells including adult mouse neural stem cells, mouse oligodendroglioma-derived stem cells and human glioblastoma multiforme-derived stem cells.[32] In contrast, a study confirming the role of miR-137 in modulation of proliferation and

Table 1. List of experimentally validated miR-137 targets

Target gene	*Full name*	*Verification method*	*Cell line*	*Biological role*	*Reference*
MITF	Microphthalmia-associated transcription factor	Luciferase assay, GFP reporter	HEK293, A375, WM852	Cell differentiation, proliferation, survival	Haflidadóttiretal *et al.*;[128] Chen *et al.*[45]
KDM1A (LSD1)	Lysine (K)-specific demethylase 1A	Western blot, luciferase assay	Neroblastosoma	Cell proliferation, growth differentiation	Balaguer *et al.*;[47] Sun *et al.*[28]
PXN	Paxillin	Western blot, luciferase assay	NSCLC	Actin-membrane attachment, cell mobility and migration	Bi *et al.*[101]
MIB1	Mindbomb E3 ubiquitin protein ligase 1	Luciferase assay	Primary neurons	Apoptosis, cell cycle	Smrt *et al.* [41]
TWIST1	Twist family BHLH transcription factor	Western	GIST-H1	Cell lineage determination/ differentiation	LL Liu *et al.*[129], S Liu *et al.*[130]
CPLX1	Complexin-1	Western, luciferase assay	HEK-293T	Synaptic vesicle exocytosis	Siegert *et al.*[73]
NSF	*N*-ethylmaleimide-sensitive factor	Western, luciferase assay	HEK-293T	Fusion of transport vesicles	Siegert *et al.*[73]
SYT1	Synaptotagmin-1	Western, luciferase assay	HEK-293T	Synaptic vesicle exocytosis	Siegert *et al.*[73]
CDK6	Cyclin-dependent kinase 6	Western, luciferase assay	U251, OSCC, HEK293	Cell cycle	Silber *et al.*;[32] Kozaki *et al.*[44]
CDC42	Cell division cycle 42	Western, luciferase assay	SW116, Lovo, Hela, AGS, MKN45	Cell cycle	Liu *et al.*;[131] Zhu *et al.*[46]
ZNF804A	Zinc finger protein 804A	Luciferase assay	HEK-293T, Be2C	Neuronal development, cell adhesion	Kim *et al.*[132]
CSMD1	CUB and Sushi multiple domains 1	Luciferase assay	HEK-293T	Potential tumor suppressor	Kwon *et al.*[62]
C10orf26	WW domain binding protein 1-like	Luciferase assay	HEK-293T	Potential tumor suppressor	Kwon *et al.*[62]
CACNA1C	Calcium channel, voltage-dependent, L type, alpha 1C subunit	Luciferase assay	HEK-293T	Regulating contraction, secretion, gene expression neurotransmission	Kwon *et al.*[62]
TCF4	Transcription factor 4	Luciferase assay	HEK-293T	Neuronal development	Kwon *et al.*[62]
RORa	Retinoic acid-related orphan receptor alpha gene	Western	SHSY5Y	Circadian rhythm, organogenesis and differentiation	Devanna *et al.*[80]
KLF4	Kruppel-like factor 4 (gut)	Western, luciferase assay	LCL, R1 ES	Development, differentiation,	Willemsen *et al.*;[37] Jiang *et al.*[39]
TBX3	T-Box 3	Western, luciferase assay	R1 ES	Development	Jiang *et al.*[39]
CTBP1	C-terminal binding protein 1	Ago2binding assay, luciferase assay	HEK293, A375	Development, proliferation	Deng *et al.*[133]
E2F6	E2F transcription factor 6	Western	OSCC	Cell cycle	Kozaki *et al.*[44]
NCOA2	Nuclear receptor coactivator 2	Western	OSCC	Cell growth, development, homeostasis	Kozaki *et al.*[44]
SPTLC1	Serine palmitoyltransferase, long chain base subunit 1	Luciferase assay	Rat primary astrocytes	Sphingolipid biosynthesis	Geekiyanage and Chan[134]
RB1 (p-Rb)	Retinoblastoma 1	Western	M23, SP6.5	Cell cycle, tumor suppressor	Chen *et al.*[45]
MAPK1 (p-ERK1/2)	Mitogen-activated protein kinase 1	Western	M23, SP6.5	Proliferation, differentiation, development	Chen *et al.*[45]
MAPK3 (p-ERK1/2)	Mitogen-activated protein kinase 3	Western	M23, SP6.5	Proliferation, differentiation, cell cycle	Chen *et al.*[45]
MET (c-Met)	Met proto-oncogene (hepatocyte growth factor receptor)	Western blot, luciferase assay	M23, SP6.5	Embryonic development, wound healing	Chen *et al.*;[45] Luo *et al.*[95]
CDK2	Cyclin-dependent kinase 2	Western	M23, SP6.5	Cell cycle regulation	Chen *et al.*[45]
EZH2	Enhancer of zeste homolog 2	Luciferase assay	HEK-293T	DNA methylation repression, embryonic development	Szulwach *et al.*[40]
KDM5B (Jarid1b)	Lysine (K)-specific demethylase 5B	Western, luciferase assay	Mouse ESC, HEK293	Histone demethylase, cancer development	Tarantino *et al.*[38]
PTBP1	Polypyrimidine tract binding protein 1	Luciferase assay	HCT116	Pre-mRNA processing, metabolism and transport	Sun *et al.*[28]
GLIPR1 (RTVP-1)	GLI pathogenesis-related 1	Western, luciferase assay	U87, HF2354 HF2359, HF2485	Differentiation, involved in cancer	Bier *et al.*[135]
MSI1	Musashi homolog 1 (Drosophila)	Western, luciferase assay	U251, Daoy, HeLa	Stem cell regulator	Smith *et al.*[97]
ESRRA	Estrogen-related receptor alpha	Luciferase assay	HepG2	Regulator of energy metabolism	Zhao *et al.*[136]
PTGS2 (Cox-2)	Prostaglandin-endoperoxide synthase 2	Western, luciferase assay	U87, LN229	Dioxygenase and peroxidase	Chen *et al.*[93]
HTT	Huntingtin	Western, luciferase assay	HEK293T	Linked to Huntington's disease	Kozlowska *et al.*[137]
CSE1L	Chromosome segregation 1-like	Western, luciferase assay	LNZ308	Nucleocytoplasmic recycling of importin-α, cell migration, secretion	Li *et al.*[94]
YBX1	Y box binding protein	Western, luciferase assay	HEK293, Ma-Mel-79b, Ma-Mel-86b	Regulation of translation, transcription, cell migration, proliferation	Luo *et al.*[95]
AKT2	V-AKT murine thymoma viral oncogene homolog 2	Western, luciferase assay	QGY-7703, SK-Hep	Protein kinase, cancer development	Liu *et al.*[129]

Table 1. (Continued)

Target gene	*Full name*	*Verification method*	*Cell line*	*Biological role*	*Reference*
FMNL2	Formin-like protein 2	Western, luciferase assay	293FT, CRC cell lines	Morphogenesis, cytokinesis, cell polarity, adhesion	Liang *et al.*[138]
AEG-1	Astrocyte elevated gene-1	Western, luciferase assay	SKOV3, OV2008	Role in RISC, miRNA functions, ontogenesis	Guo *et al.*[111]
Wnt7a	Wingless-type MMTV integration site family member 7A	Western	HEK293	Oncogenesis and development	Hollins *et al.*[42]
Gpr88	G-protein-coupled receptor 88	Western	HEK293	Neuron development	Hollins *et al.*[42]
PAQR3	Progestin and AdipoQ receptor family member III	Western, luciferase assay	T24	Raf kinase regulation	Xiu *et al.*[112]
FXYD6	FXYD domain containing ion transport regulator 6	Western, luciferase assay	HEK293T	Na+/K+-ATPase regulation	Li *et al.*[110]
PTN	Pleiotrophin	Western, QPCR	PANC-1, MIA, PaCa-2	Apoptosis, cell proliferation	Xiao *et al.*[109]

differentiation concluded the opposite effects in adult neural stem cells (aNSCs) by showing that miR-137 enhanced proliferation and inhibited differentiation through posttranscriptional suppression of Ezh2.[40] These results suggest that there might be a context-dependent role for miR-137 in neural stem cells. Also, miR-137 was identified to have an important role in regulating neuronal maturation. Smrt *et al.* reported that Mib1, known to be associated in neurodevelopment, is negatively modulated by miR-137 through which dendritic morphogenesis, phenotypic maturation and spine development were affected in newborn neurons of the adult hippocampus[41] (Figure 4b). We recently analyzed the microRNA and mRNA expression in midbrain and forebrain in the rat embryo and observed upregulation of miR-137 across brain development.[42] We further identified two neural development-associated genes, Wnt7a and Gpr88, as direct targets of miR-137 using luciferase assay. Interestingly, a recent study revealed that embryonic development is dependent on the presence of at least one functional allele of *MIR137*,[43] with embryonic lethality occurring in all homozygous (−/−) embryos for miR-137 allele. No phenotype was observed in miR-137 heterozygous mice presumably as a consequence of dosage compensation from the remaining allele, as there was no difference in mature miRNA expression compared with the homozygotes.

Taken together, these results suggest that miR-137 has an important role during neural development through regulation of target genes associated with neural stem cell proliferation and differentiation. These studies further support miR-137s contribution to the regulation of transition from pluripotentency to differentiated states. Given miR-137s involvement in these processes as well as apoptosis, it is perhaps not surprising that its depletion is also associated with the development and progression of cancers (discussed in detail below).

REGULATION

MiRNAs are important regulators of gene expression, however, they can also modify other epiphenomena by modulating the expression of target gene networks in epigenetic mechanisms. Some miRNAs, known as epi-miRNAs, have even been implicated more directly through their capacity to guide some of the enzymes associated with modulation of epigenetic machinery. MiRNA expression can also be affected by epigenetic modulation of their host gene promoters.[31]

The *MIR137* gene is itself highly regulated by large CpG island embedded in the upstream promoter region of its gene located on chromosome 1p22.[44] These have been shown to be modified by DNA-hypermethylating agents, which result in suppression of miR-137 transcription.[44] For instance, Chen *et al.* established that miR-137 is suppressed epigenetically in uveal melanoma cell lines and treatment with 5-aza-dC, a DNA methylation inhibitor and/or TSA, a histone deacetylase inhibitor, could restore the expression of miR-137.[45] Another study on miR-137 has indicated that it was also silenced as a result of aberrant DNA methylation in oral squamous cell carcinoma.[44] Similarly, evidence from a report in glioblastoma validated that miR-137 was silenced by hypermethylation.[32] Consistent with previous studies, Zhu and colleagues found that levels of miR-137 were suppressed in non-small cell lung carcinoma (NSCLC) but restoration of activity was observed after treatment with DNA-hypomethylating agents.[46] Real-time results showed that miR-137 transcripts increased up to eight-fold following 5-aza-dC treatment, and up to nine-fold in cells treated with both 5-aza-dC and TSA, indicating the role of epigenetic modification of regulatory sequences in CpG islands in miR-137 silencing. Further supporting data from studies on colorectal cancer,[47] gastric cancer[48,49] and squamous cell carcinoma of the head and neck[50,51] demonstrated methylation-silencing of miR-137. In mouse adult neuronal stem cells, the expression of miR-137 is affected through epigenetic regulation

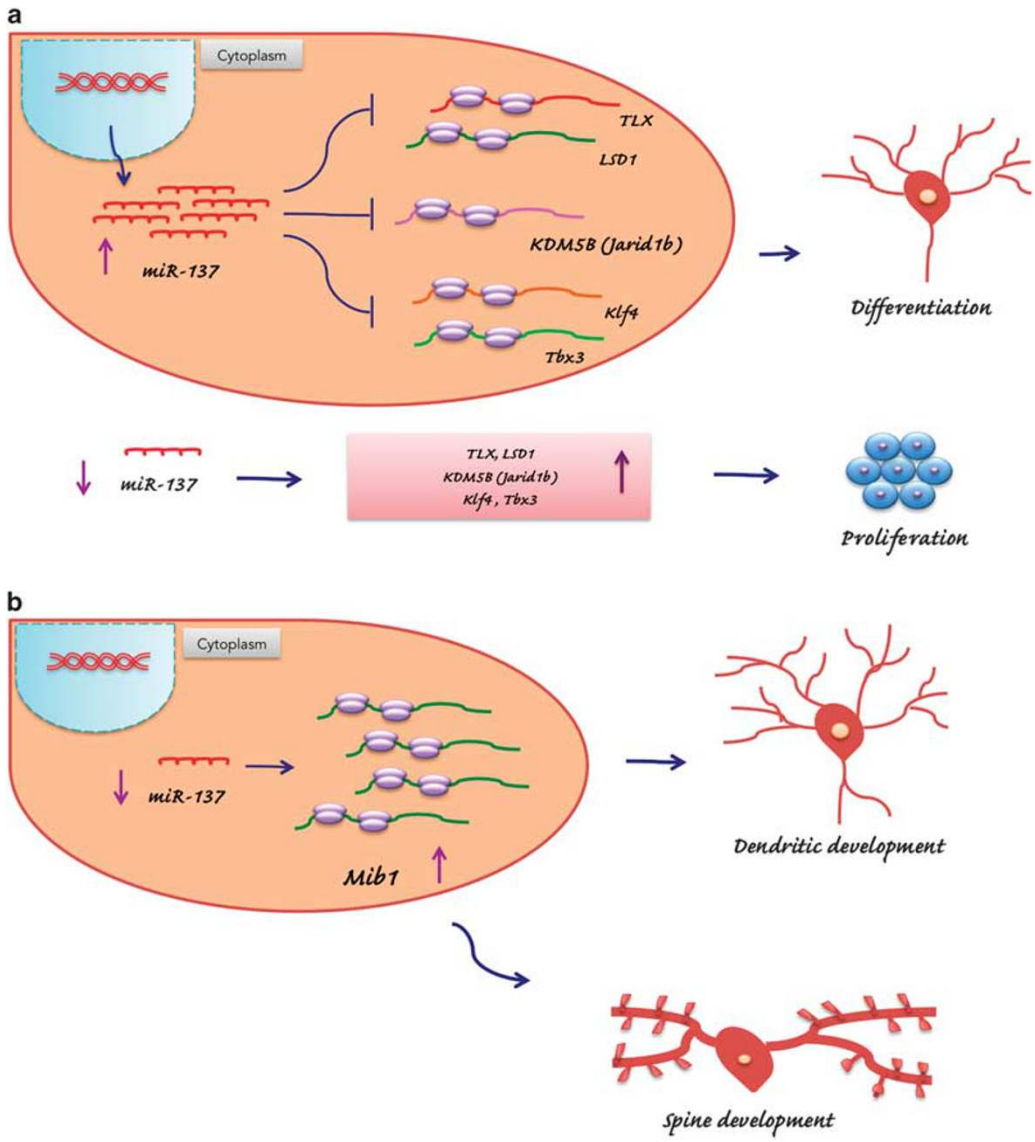

Figure 4. The impact of miR-137 on neural differentiation, proliferation and maturation in ESCs and newborn neurons. (**a**) Upregulation of miR-137 can suppress target mRNAs such as TLX, LSD1, KDM5B and Tbx3 resulting in the neural stem cell move to cell differentiation, whereas low levels of this miRNA cause an increase in target genes expression that lead to cell proliferation.[28,38,39] (**b**) MiR-137 regulate dendritic complexity and spine numbers by targeting Mib1 gene in newborn neurons.[41] ESC, embryonic stem cells; miRNA, microRNA.

mediated by the DNA methyl-CpG-binding protein MeCP2,[52] and transcription factor Sox2.[40] It was shown that direct binding of MeCP2 and Sox2 to the regulatory region of miR-137, in the 2.5 kb upstream region, is essential for proper regulation of miR-137 in aNSCs.[40] These findings strongly implicate GpC methylation and silencing as an important mechanism in the deregulation of miR-137.

MiR-137 activity is also involved in the modulation of genes interacting in epigenetic pathways. For example, Szulwach *et al.* discovered that miR-137 modulated the levels of Ezh2 directly in aNSCs.[40] Ezh2 is a H3-K27 methyltransferase and component of the polycomb group (PcG) proteins, which are known to remodel chromatin and induce epigenetic silencing. PcG proteins function by creating and maintaining repressive chromatin environments, allowing cell/tissue-specific genes to be primed for expression.[53,54] Overexpression of miR-137 was able to posttranscriptionally suppress the expression of Ezh2 leading to a global decrease in histone H3 trimethyl lysine 27.[40] MiR-137 was also shown to target the downstream transcriptional co-repressor, histone lysine-specific demethylase 1 (LSD1).[28] This is important in TLX signaling, which can induce feedback repression of miR-137 through the recruitment of LSD1 to the miRNA genes promoter. Similarly Jarid1b, also known as KDM5b (expressed in ESCs and in the very early stages of embryonic development) was shown to be a direct target of miR-137.[39] Jarid1b specifically demethylates lysine 4 of histone H3 (meH3K4), which leads to inhibition of RNA polymerase and transcription factor binding within promoter elements,[55]), thus repressing gene transcription. Collectively, these findings suggest that miR-137 has a significant role in epigenetic regulation and its dysregulation can affect or be affected by epigenetic modulation.

PSYCHIATRIC DISORDERS

Prior to any neurological disease association, several groups provided evidence to suggest that miR-137 is associated with the regulation of adult neurogenesis, dendritic development and neuronal maturation[40] as well as control of the dynamics between

neural stem cell proliferation and differentiation during neural development.[28] With this background, it was perhaps not surprising that miR-137 has been reported to be genetically associated with mental illness. This is supported by molecular neuropathology and expression analysis in peripheral blood.

MiR-137 in psychotic disorders

SZ is a severe and heritable psychiatric disorder affecting ~1% of the general population worldwide,[56] which shares some genetic risk factors and abnormalities in brain structure with BD.[57,58] Before the discovery of a genetic link with SZ, variant gene-sets associated with increased BOLD activation in functional imaging of SZ patients, were observed to be enriched with miR-137 target genes.[59] In the first large-scale mega genome-wide association studies of SZ, involving more than 20 000 samples, the *MIR137* host gene (MIR137HG) was implicated as a susceptibility locus through its proximity to the associated tag single-nucleotide polymorphism (SNP) rs1625579.[29] This association was also supported in a cohort of Han Chinese[60] and further replicated in Europeans.[61] In addition, four predicted miR-137 target genes including TCF4, CACNA1C, CSMD1 and C10orf26 were the other associated loci, suggesting that convergent pathways linked by the miRNA may contribute to this complex neuropsychiatric disorder. The 3′ UTR of these targets were subsequently shown to be modulated by miR-137 in the context of a reporter gene assay.[62] Pathway analyses indicated several genes with predicted miR-137 target sites were significantly enriched among smaller association *P*-values for SZ. Further upstream, rs1198588 was shown to be a significant local expression quantitative trait locus (eQTL) for *MIR137* and *DPYD*—a protein-coding gene in the same linkage disequilibrium block as *MIR137* and also predicted target of miR-137.[61] More recently in the landmark mega genome-wide association studies (almost 37 000 cases and 113 000 controls) 108 independent SZ risk loci reasserted the *MIR137* association (rs1702294, $P = 3.4 \times 10^{-19}$).[63] Again, gene set analysis of this data also showed the enrichment of putative miR-137 targets for SZ associations.[63]

In candidate-based phenotypic studies, the risk allele was shown to be associated with lower P300 amplitude.[64] Carriers also displayed less positive symptom (lower OPCRIT scores $< 10^{-5}$) and more cognitive deficits involving episodic memory and attentional control in a cohort of SZ, schizoaffective disorder and bipolar affective disorder.[65] Similarly, carrier considered high risk for SZ and BD, had reduced response in the right posterior medical frontal gyrus region in functional magnetic resonance imaging. Moreover, the SZ high-risk group had differential activation in the left amygdala and left pre/postcentral gyrus, suggesting the susceptibility allele may affect SZ more specifically.[30] Van Erp and colleagues performed a study on 111 subjects including 44 SZ patients and 61 healthy controls to realize the functional role of miR-137 locus risk genotype.[66] Using and Sternberg item recognition paradigm (SIRP) data from participants, they found that those with the rs1625579 TT genotype had significantly higher left dorsolateral prefrontal cortex activation than subjects with the GG/GT genotypes, suggesting the association of miR-137 risk genotype with the SZ risk phenotype dorsolateral prefrontal cortex hyperactivation. In support of the functional impact of miR-137 risk variant, it was established that it was predictive of phenotypic variability. A significantly earlier age-at-onset of psychosis was found for 'TT' homozygotes compared with protective G-allele carriers.[67] Also, brain structure of SZ subjects was affected by the risk genotype, such that those with the miR-137 risk variant had lower white matter integrity, also decreased hippocampi and larger lateral ventricle volumes, while patients carrying the protective allele showed no difference from healthy controls in this regard. In post-mortem analysis, miR-137 has not been shown to be differentially expressed in SZ including studies in our own lab.[68,69] Guella and colleagues, however, showed that while miR-137 was not differentially expressed in the disorder, the levels were significantly reduced in the common risk variant when stratified by the rs1625579 genotype.[70] Our team investigated the *MIR137* SNP association with specific phenotypic characteristics of SZ indicating that the risk genotype was able to subtype SZ.[71] Grade of Membership analysis yielded two patient categories including cognitive deficit group and cognitive spared group, with 'G' allele predicting cognitive deficit group status in patients with significant negative symptoms. This was surprising given that the T allele is associated with the risk of SZ. Further investigation of the risk haplotype associated with the tag SNP rs1625579 using promoterless luciferase reporter assay, suggest that miR-137 expression levels are affected by other functionally implicated SNPs including rs2660304 which are in linkage disequilibrium.[72,73] Overexpression of miR-137 in a human neural stem cell line led to differential expression of the genes involved in pathways implicated in SZ including major histocompatibility complex, synapses, FMRP interacting RNAs and calcium channels after the 48 h, providing more support for a role in the etiology of the disorder.[74]

Major depression

MiR-137 has also been shown to have anti-depressive effects in a post-stroke depression rat model.[75] Zhao *et al.* found that miR-137 levels were significantly lower in the brain and peripheral blood compared with controls. Exogenous delivery of miR-137 *in vivo* led to improvement of behavioral changes in post-stroke depression rats.[75] These impacts were shown to be as a result of miR-137's suppressive role on Grin2A protein through binding to Grin2A mRNA. MicroRNA expression profiling in prefrontal cortex of depressed suicide subjects demonstrated that miR-137 is down-regulated in patients suggesting the involvement of miR-137 in mood disorders.[76] In addition, a risk allele within CACNA1C, a target gene of miR-137, is associated with the risk of major depression as well as SZ and BD.[77] Other reports identified statistical association between this miR-137 target gene, CACNA1C, and major depressive disorder.[78,79]

Autism spectrum disorders

The MIR137 gene has also been implicated in autism spectrum disorders (ASDs). In a study by Devanna and Vernes provided support for MIR137 as an autism candidate by showing that the RORa gene is regulated directly by miR-137 through targeting its 3′ UTR in a site-specific manner.[80] RORa, a novel autism candidate gene, is known as a transcription regulator encoding a ligand-dependent orphan nuclear receptor whose target genes are associated with susceptibility to ASDs and was found to be important in pathways implicated in ASDs.[81] Further analysis demonstrated that two synaptic genes, SHANK3 and NRXN1, previously identified as autism candidate genes were also putatively targeted by miR-137.[81] SHANK3 is involved in synapse formation and function and NRXN1 was found as a risk factor for both autism and SZ with a SNP associated with changes in frontal white matter volume—an endophenotype common to both disorders.[82] Findings from other genome-wide association studies have identified SNPs in the human miR-137 gene locus that are associated with an increased risk of SZ and ASDs.[61,83] These findings were supported with reports that autism spectrum disorders are related to microdeletions of this region.[37,84]

Huntington's disease

Recent discoveries implicated miRNA in posttranscriptional dysregulation in Huntington's disease (HD) and many crucial neural-specific miRNAs are aberrantly repressed in this disorder.[85] REST is one of the first transcription factors to be shown to

modulate miRNA transcription, appearing to be an important regulator of neuron-specific miRNAs. Evidence from work on HD, using Hdh7/7 and Hdh109/109 cells, used extensively as a cellular model of molecular dysfunction in HD, identified several miRNAs, including miR-137, whose aberrant repression was directly mediated by REST.[86] MiR-137 was upregulated in Hdh109/109 cells by REST, whereas REST knock down resulted in decreased miR-137 expression, suggesting that REST is a direct regulator of this miRNA. In the presence of muHtt, mutated form of Htt causing HD, REST protein translocates to the nucleus where it represses transcription of its target genes that are significant for nervous system development and function such as miR-137.

Rett syndrome

A genome-wide analysis in a mouse model of Rett syndrome found that upregulation of miRNAs, including miR-137, were implicated in its pathoetiology.[87] This disorder is caused by the mutations in MECP2 gene, which normally negatively regulate the expression of the aberrant miRNAs in brain by directly targeting their methylated promoters. Combined ChIP-chip and expression analyses suggested a model in which Mecp2 directly binds to DNA methylated regions within promoter of miRNA and acts as a transcriptional repressor. Furthermore, in addition to miR-137, several Mecp2-regulated miRNAs are implicated in regulation of dendritogenesis and synapse formation/maturation,[88,89] therefore dysregulation of synapse-localized miRNAs such as miR-137 may contribute to neurological disorders including Rett syndrome. Mecp2-regulated miRNAs, including miR-137, in neurons therefore may act as a critical mechanistic link between nucleus-localized Mecp2 and cytoplasmic/synaptic proteins.

Intellectual disability

Chromosomal microdeletion of 1p21.3 encompassing miR-137 and DPYD have also been observed in ID, with a corresponding reduction of precursor and mature miR-137 and significantly increased levels of downstream targets including MITF, EZH2 and KLF4 in patients compared with controls.[37]

These genetic association, expression and functional studies support a role for miR-137 pathways in neural processes and neurocognitive disorders. This is consistent with molecular systems analysis of miR-137 implicating pathways in neurogenesis and brain development. High expression of miR-137 have been reported to be present at the synapse where it has a role in controlling dendritic spine maturation and density.[41] Alteration of dendritic spine number, density and volume have been shown in SZ and ASDs, with dendritic spine reduced in SZ, but increased in ASD.[90,91] MiR-137 therefore appears to be a central network hub with significant implications for its dysregulation in the etiology of multiple psychiatric and neurocognitive disorders.

CANCER

Several miRNAs have been implicated in the pathogenesis of human cancer. These oncogenenic-miRNA (Onco-miRs) or tumor suppressor-miRs (Ts-miRNAs) are associated with the early stages of carcinogenesis and may also participate in progression and metastasis.[92] This is supported by miRNA expression-profiling studies showing a reduction in miR-137 expression in the pathogenesis of numerous malignancies. For instance, in glioblastoma multiforme, which is the most frequent and malignant of primary brain tumors, a cohort of microRNAs, including miR-137, were identified to be significantly downregulated.[32] By contrast its overexpression led to inhibition of cell proliferation and invasion in glioma cell lines, perhaps as a result of inverse regulation of Cox-2.[93,94] Li *et al.* further established that this miR-137 negatively regulated cell viability, anchorage-independent growth and invasion through modulation of CSE1L expression.[94] Functional studies in several melanoma cell lines also revealed that miR-137 was able to inhibit melanoma cell invasion, migration, proliferation and induced apoptosis via downregulation of multiple target genes including transcription factor MITF and the oncogenes c-Met, YB1, EZH2 and PAK2, suggesting miR-137 involvement in several significant pathways in melanoma development and progression.[95,96] Lower miR-137 expression contributed to poor survival in stage IV melanoma patients.[95] MiR-137 appears to also act as a tumor suppressor in colon cancer.[97] MSI1, a stem cell regulator with high expression in colorectal cancer was downregulated by miR-137 in colon tumors leading to reduction in cell growth, colony formation and tumorsphere growth *in vitro* as well as inhibition of tumor growth *in vivo*. Restoration of miR-137 in these cell lines negatively regulated two significant oncogenic signaling pathways, Wnt and Notch, which are known to be associated with colorectal cancer progression and modulated by MSI1. Quantitative PCR analysis of a large group of miRNAs in colorectal cancer also indicated that miR-137 is downregulated compared with normal tissue.[98] Similarly, genome-wide miRNA expression profiling of a large cohort of breast tumor samples observed significant change in the levels of miR-137 as well as 12 other miRNA compared with normal tissue.[99] Moreover, examination of a large number of miRNAs by microarray and then qPCR assays placed miR-137 among the significantly downregulated miRNAs in three different lung adenocarcinoma tumors.[100] Bi *et al.* explored the regulatory function of miR-137 in progression of NSCLC discovering that miR-137 expression was negatively correlated with cell proliferation, cell migration and invasion, and was able to induce cell apoptosis in NSCLC cell lines through regulation of a direct target gene PXN,[101] which is implicated in many human tumors[102,103] and involved in various physiological processes such as gene expression, tissue remodeling, cell proliferation and survival.[104,105] MiR-137 expression was low in lung cancer inducing G1 cell cycle arrest and suppressed cell growth both *in vivo* and *in vitro*.[46] Overexpression of miR-137 was reported to decrease the expression of Cdc42 and Cdk6 and their immediate downstream effectors including cyclin D1, p-ERK1/2 and p-Rb, suggesting that miR-137 acts through the inhibition of Cdc42 and Cdk6 in lung cancer cells. In addition, expression profiles of human miRNAs in some tumor-derived cell lines,[106] neuroblastoma[107] and high-grade astrocytic tumors[108] validated the decreases in miR-137 expression in tumor cells compared with controls, further supporting the role of miR-137 in pathogenesis of cancer. A role for miR-137 as a tumor suppressor is evident in several other malignancies including, pancreatic cancer,[109] osteosarcoma cancer,[110] gastric cancer,[48] oral cancer[50] and ovarian cancer.[111]

With the exception of bladder cancer and thyroid cancer,[112–114] these findings show that a reduction of miR-137 is an important influence in the pathogenesis of cancer. In many cases it seems miR-137 downregulation is caused by DNA hypermethylation, suggesting that epigenetic modulation might be more significant than genetic mechanisms in oncological disorders.

CLINICAL APPROACH

The discovery of miRNA's role in cellular networks and disease has opened new possibilities in detection, diagnosis and treatment of complex disorders. This concept is also supported in several studies identifying promising miRNA candidates for diagnosis, prognosis and as therapeutic agents for clinical application.[115–117] Restoration a miRNA function has been accomplished previously using synthetic miR-mimics or vector-based overexpression and these strategies could be employed for the clinical modulation of miR-137, which is downregulation in both cancer and psychiatric disorders. More specifically, intellectual disability associated with microdeletion and haploinsuficiency of miR-137 could be treated by exogenous supplementation in this way. Overexpression of

mir-137 may also improve outcomes in ASD by reducing RORa expression. In SZ and BD where a common variant is associated with reduced expression, replacement of the miRNA may prevent onset or alleviate some of the symptoms where deficiency is indicated. Interestingly, delivery of miR-137 *in vivo* led to improvement of behavioral changes in post-stroke depression rats.[75]

In addition to supplementing with synthetic miR-137 or a transgene expression system, it may be possible to pharmacologically modulate miR-137 expression using small molecules. For example, it was shown that chromatin-demethylating agents, which transactivate miR-137 expression, resulted in suppression of NSCLC proliferation.[46] Capecitabine chemoradiotherapy of rectal cancer was also shown to upregulate miR-137 in the most advanced T-stage.[118] An indication of the therapeutic benefit of miR-137 was demonstrated in a study by Xiao *et al.*, showing that upregulation of miR-137 increased sensitivities to chemotherapy reagent 5-FU in pancreatic cancer cells and reduced tumor weight and size *in vivo*.[109] Similarly, modulation of miR-137 levels in the early stages or acute phase of neurodevelopmental disorders might help to alleviate these diseases.

There are a number of microRNA being pursued for therapeutic application, highlighting the feasibility of these molecules clinically. For example, delivery of miR- 34 and let-7 mimics inhibited tumor development in mouse models of lung and prostate cancers.[119–121] Some other specific miRNAs currently in development as clinical candidates include miR-155, miR-21 and miR-33.[122] Although miR-137 also presents as a promising candidate for therapeutic application, it will require significantly more preclinical testing *in vivo*, particularly for application in the central nervous system, where the blood–brain barrier remains as a significant hurdle for the delivery of large molecules and gene constructs.

FUTURE PERSPECTIVES

It is clear that this miR-137 is of considerable interest both in terms of its biological processes and association with major diseases. There are still many unexplored questions that arise from this exciting research, for example, a huge number of miR-137 target genes have been predicated,[35] whereas only a small proportion have been investigated and confirmed. Pathway analysis of targets implicated several aspects of nervous system function and development associated with SZ, including ephrin receptor signaling and axonal guidance signaling as well as synaptic long-term potentiation.[123–125] Although recent studies provide compelling link between MIR137 variants, such as rs1625579, and psychiatric disorder, the mechanisms causing dysregulation of miR-137 is not fully understood. Functional analysis of the variants in linkage disequilibrium with this tag SNP should provide new insight into this question. Siegert *et al.* provided evidence supporting a variant upstream (rs2660304) while also showing that this miRNA is involved in presynaptic plasticity through the regulation of several protein targets by miR-137.[73] Surprisingly, developmental disruption of miR-137 in mice led to embryonic lethality,[43] whereas heterozygous knockouts had no phenotype. Alternatively, we recently demonstrated that neurodevelopmental suppression miR-137 in the zebrafish resulted in severe sensorimotor deficits.[126] This phenotype was not associated with any obvious change in the neuroanatomy or histology of the animals. More fine control of the miR-137 deficit in these models and more neurophysiological analysis will provide new insight to the biological basis of these behavioral phenotypes. Previously we observed that miR-137 expression was increased in telencephalon between E12 and E19 in the rat, whereas levels in the mesencephalon were fairly consistent from the earliest embryonic age.[42] Although this suggested there is significant variation in the temporospatial expression pattern for miR-137, more details are required to better understand the expression of this molecule at different stages of development for various areas within cortical and subcortical structures.

CONCLUSIONS

In this review, we have outlined the compelling research suggesting that miR-137 is a significant network figure in the regulation of both neurodevelopmental processes and cancer biology. The development and maturation of neurons in embryonic and adult stem cells both *in vivo* and *in vitro* seem to be particularly sensitive to the expression of miR-137, with upregulation of miR-137 making a shift from proliferation to differentiation. The role of miR-137 in the induction of cell differentiation and inhibition of proliferation are also observed in cancer biology, suggesting tumor suppressive effects of this miRNA and significance for its repression in cancer biology. Interestingly, epidemiological studies have reported a potential link between SZ and cancer incidence, with these patients having a differential cancer risk.[127] In addition to environmental, pharmacological and psychosomatic factors, genetic background was strongly implicated in this association and may possibly involve *MIR137*. Regardless, this molecule has a significant function in several neuropsychiatric/neurocognitive/oncological disorders and consequently may have great potential as a biomarker and in treatment of human diseases where dysregulation of this gene or its pathways are a factor. However, to reach this goal more exploration is required to completely understand the molecular mechanisms involved in disorders affected by this fascinating small RNA.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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