NeuroMolecular Medicine (2019) 21:97–109
https://doi.org/10.1007/s12017-019-08535-9

REVIEW PAPER

MiR-34 and MiR-200: Regulator of Cell Fate Plasticity and Neural Development

Abhishek Jauhari[1,2,3] · **Sanjay Yadav**[1]

Received: 5 September 2018 / Accepted: 1 April 2019 / Published online: 8 April 2019

Abstract

Studies from last two decades have established microRNAs (miRNAs) as the most influential regulator of gene expression, especially at the post-transcriptional stage. The family of small RNA molecules including miRNAs is highly conserved and expressed throughout the multicellular organism. MiRNAs regulate gene expression by binding to 3′ UTR of protein-coding mRNAs and initiating either decay or movement of mRNAs to stress granules. Tissues or cells, which go through cell fate transformation like stem cells, brain cells, iPSCs, or cancer cells show very dynamic expression profile of miRNAs. Inability to pass the developmental stages of Dicer (miRNA maturation enzyme) knockout animals has confirmed that expression of mature and functional miRNAs is essential for proper development of different organs and tissues. Studies from our laboratory and elsewhere have demonstrated the role of miR-200 and miR-34 families in neural development and have shown higher expression of both families in mature and differentiated neurons. In present review, we have provided a general overview of miRNAs and focused on the role of miR-34 and miR-200, two miRNA families, which have the capability to change the phenotype and fate of a cell in different tissues and situations.

Keywords MicroRNAs · Cell fate · Brain development · Differentiation · MiR-34 and miR-200

Introduction

RNA molecules, which do not have protein-coding capacity, but have the capacity to regulate protein synthesis are termed as regulatory non-coding RNAs (ncRNAs). Regulatory ncRNAs have been identified as molecular managers of different developmental and evolutionary processes in multicellular organisms. Long ncRNAs (lncRNAs), small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), enhancer RNAs, promoter-associated RNAs, circular RNAs (CircRNAs), and microRNAs (miRNAs) are the major types of ncRNAs (Mattick and Makunin 2006; Stefani and Slack 2008; Mattick 2001). Among all the classes of ncRNAs, miRNAs have been studied extensively in development and evolution of multicellular organisms. Discoveries of miRNA-mediated gene regulation in the last decade have greatly enhanced our understanding towards the mechanisms of regulation of gene expression. MiRNAs play essential role in stemness, brain development, iPSCs, epithelial-to-mesenchymal transformation (EMT), and maturation of different cell types (Kapranov et al. 2010; Gustincich et al. 2006; Aberdam et al. 2008; Coolen and Bally-Cuif 2009; Singh et al. 2014; Alvarez-Garcia and Miska 2005; Kalluri and Weinberg 2009). Role and regulation of miRNAs in brain development have been studied more extensively than any other functions of miRNAs. The potential of miRNAs in the regulation of individual gene expression, as well as a network of genes, provides the capability to brain cells specifically neurons to control gene expression in spatiotemporal fashion, which is the prerequisite for the shaping of developing brain (Kiecker and Lumsden 2005). In developing brain, progenitor cells born and differentiate in different lineages, which migrates to their final destination and generate neurites and axons (Tau and Peterson 2010). Branching

✉ Sanjay Yadav
sanjay@iitr.res.in; sanjayitrc@gmail.com

1 Developmental Toxicology Laboratory, Systems Toxicology and Health Risk Assessment Group, CSIR-Indian Institute of Toxicology Research (CSIR-IITR), Vishvigyan Bhawan, 31 Mahatma Gandhi Marg, Lucknow, UP 226001, India

2 Academy of Scientific and Innovative Research (AcSIR), CSIR-IITR Campus, Lucknow, India

3 Present Address: Neuroapoptosis Laboratory, Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA

and establishment of synaptic connections deliver the basic structure to encode information for the rest of life (Andersen 2003). Every step of brain development from differentiation to maturation of neurons is tightly regulated and required a specific network of gene regulatory mechanisms. Development of prenatal and postnatal brain is known to involve the coordinated expression of thousands of genes to achieve the regional specificity (Chinwalla et al. 2002; Colantuoni et al. 2011; Kang et al. 2011). In adults, functional regions of the brain have been shown to have unique gene expression, which is region specific (Sandberg et al. 2000; Datson et al. 2001). Region- and stage-specific gene expression in developing as well as in adult brain suggested the existence of unique gene regulatory mechanism network (He and Rosenfeld 1991). Brain is known to express maximum number of unique miRNAs among all the different organs, which suggest their abundance must have some metabolic and physiological significance (Motti et al. 2012). Several previously published studies from our lab and elsewhere have been reported that miRNAs are the crucial regulators of basic process of brain development like neuronal proliferation, neuronal differentiation, and neuronal apoptosis (Pandey et al. 2015a, b; Singh et al. 2014; Yadav et al. 2011, 2015; Jauhari et al. 2017; 2018a, b). Knockout studies of Dicer gene, a ribo-endonuclease required for generation of mature miRNAs from precursor miRNAs, have shown that Dicer is essential for development because Dicer knockout mice were not viable and unable to cross the gastrulation period (Bartel 2004; Bernstein et al. 2003). Depletion of Dicer gene in the cerebral cortex reduced the number of progenitor cells, the thickness of cortical walls, and disrupted neuronal differentiation (Kawase-Koga et al. 2009). The importance of the miRNAs in regulation of different phases of neurogenesis as well as gliogenesis has been revealed by Dicer knockout studies (Kawase-Koga et al. 2009). In addition to the brain development, essential role of miRNAs has been extensively demonstrated in proliferation, differentiation and maintenance of stem cells, iPSCs generation, and epithelial-to-mesenchymal transformation (EMT) (Gangaraju and Lin 2009; Miyoshi et al. 2011; Gregory et al. 2008). It seems that miRNAs have more influential roles in situations of cell fate determinations like future of stem cells, transformation of epithelial to mesenchymal cells, generation of mature and differentiated neurons from proliferative neural stem cells (Karp and Ambros 2005; Ivey et al. 2008). In the present review, we have provided a general view on miRNAs and focused on miR-34 and miR-200 families, which have been reported to regulate cell fate determination in several different types of cells.

Regulatory Non-coding RNAs

Regulatory ncRNAs are known to regulate protein synthesis at transcriptional or post-transcriptional or translational level either in direct or indirect fashion (Huang and Zhang 2014). MiRNAs and short-interfering RNAs (siRNAs) are examples of direct regulator, whereas circular RNAs (circRNAs) are an example of indirect regulator. An interesting example of indirect gene regulation is ciRS-7, which has several binding sites for miR-7 and functions as 'molecular sponge' for endogenous miR-7 (Lukiw 2013; Burmistrova et al. 2007; Loring et al. 2001). Another class of regulatory RNAs molecule, which is reported by several studies is long non-coding RNAs (lncRNAs), which regulate gene expression in epigenetic fashion, by guiding specific genomic modifiers at specific genomic locations. Studies have suggested that expression of these regulatory ncRNAs is dramatically increased in multicellular organisms (Amaral and Mattick 2008; Stefani and Slack 2008). Moreover, regulatory ncRNAs have shown to regulate gene expressions and play a crucial role in the developmental processes of complex organisms (Amaral and Mattick 2008). According to the reported function and structure, regulatory ncRNAs fall in the following types:

(a) miRNAs
(b) CircRNAs
(c) Long non-coding RNAs (lncRNAs)
(d) Small interfering RNAs
(e) Piwi-interacting RNAs
(f) Enhancer RNAs and promoter-associated RNAs

MiRNAs

MiRNAs are the most extensively studied class of ncRNA molecules, which are predicted to target more than 60% of protein-coding genes in mammals (Muljo et al. 2010). Mature miRNAs are 20–22 nucleotide in length and bind with 3′ UTR of target mRNAs through 8–9 nucleotide long seed sequence (Kim 2005). Binding of miRNAs with 3′ UTR of mRNAs in sequence-specific manner either halts the protein translation or degrades the mRNAs. Lee et al. (1993) were the first to discover lin-4-like RNAs, which regulate the developmental timing of *C. elegans,* but do not code for a protein instead produce a pair of small RNAs (Lee et al. 1993). Since then, thousands of miRNAs have been identified in almost all metazoans like flies, worms, mammals, and plants. MiRNAs are identified as well-conserved ncRNAs both in plants and animals and demonstrated to have a regulatory role in evolution (Axtell and Bartel 2005; Tanzer and Stadler 2004; Chen

and Rajewsky 2007). Similar to siRNAs, miRNAs also operate through RNA interference (RNAi) pathway, except that miRNAs derive from regions of short hairpins RNAs, whereas siRNAs originate as double-stranded RNA (Bartel 2004). Combinatorial regulation is a unique feature of miRNA-mediated mechanism of gene expression regulation, where a single miRNA targets and regulates hundreds of different mRNAs, and a single mRNA can be regulated by several miRNAs (Friedman et al. 2009; Rajewsky 2006; Krek et al. 2005). Regulatory role of miRNAs has been demonstrated in regulating cell differentiation, cell proliferation, apoptosis, developmental process, neurodegeneration, and in almost all the known physiological and cellular processes.

How to Name miRNAs?

miRNAs are named according to recommendations made by Ambros et al. (2003). Following are the salient features of the nomenclature system suggested by Ambros et al. (2003).

a. Name of any miRNAs has to be written as hsa-miR-123, where the first three letters that is 'hsa' in this example signify the organism, while 'miR' denotes mature miRNAs, and number-123 for its order of discovery. Precursor miRNAs are written as 'mir' instead of 'miR' as in mature miRNAs.
b. It has been recommended that numbering of miRNA genes should be simply sequential. For example, if anyone discovers a new miRNA than it would be numbered just after the last published miRNA. However, if identified miRNA sequence is identical to previously reported miRNA in a different organism, then it is suggested to name your sequence similar to the previous one.
c. If two identical miRNAs are expressed by two distinct genomic locations and have two different precursor sequences, then they will be named as hsa-miR-123-1 and hsa-miR-123-2.
d. If two closely related miRNAs differ only in one or two nucleotides and expressed from two different precursor molecules, then they would be suffixed with a lowercase letter like miR-123a and miR-123b and so on. These miRNAs are considered as a member of one miRNA family.
e. If two miRNAs are originated from the same predicted precursor molecule and their relative abundance clearly shows that which one is predominantly expressed miRNA, then mature miRNA sequences are named as miR-123 (the predominant miRNA) and miR-123* (from the opposite arm of the precursor). If both molecules are expressed similarly and predominance is not clear, then these miRNAs are named as miR-123-5p (from the 5′ arm) and miR-123-3p (from the 3′ arm).
f. The lin-4 and let-7 are exempted from this nomenclature system due to their historical significances. New submissions that are homologs to lin-4 and let-7 also acquire similar old names.

Roles of miRNAs

MiRNAs are first identified for their role in the regulation of developmental timing in *C. elegans* (Lee et al. 1993). Several studies have demonstrated the crucial role of miRNAs in the differentiation of cells; the first evidence was provided by studies of Kawasaki and Taira (2003). They reported the role of miR-23 in targeting Hes1 gene in retinoic acid (RA)-induced neuronal differentiation of NT2 cells (Kawasaki and Taira 2003). O'Donnell et al. (2005) has demonstrated first time the role of miRNAs in the regulation of cell-cycle progression and cell division and reported that miR-17 and miR-20 directly target E2F expression and regulate cell-cycle progression (O'Donnell et al. 2005). Role of miRNAs is well established in the regulation of apoptosis and in this context the first evidence was published by Brennecke et al. (2003); they reported that miR-bantam miRNAs is a potential regulator of apoptosis in Drosophila (Brennecke et al. 2003). Discoveries of the last decade have well established the regulatory role of miRNAs in cell fate determination, cell differentiation, cell proliferation, cell-cycle regulation, and cell apoptosis (Chen and Hu 2012; Hwang and Mendell 2006; Carleton et al. 2007; Alvarez-Garcia and Miska 2005; Bhaskaran and Mohan 2014). Moreover, the role of miRNAs has also been extensively studied in developmental processes in different organisms ranging from nematodes to mammals (Bhaskaran and Mohan 2014).

Role of miRNAs in Brain Development

Global miRNA profiling and Dicer knockout/knockdown studies have provided substantial evidence for the essentiality of miRNA expression during brain development (Petri et al. 2014). Krichevsky et al. (2003) were the first to report the regulation of miRNAs during brain development (Krichevsky et al. 2003). Using different cellular models of neuronal differentiation (SH-SY5Y, PC12, IMR32, N2a), researchers have identified dramatic up and downregulation in the expression of several miRNAs in differentiated neurons (Singh et al. 2014; Jauhari et al. 2017; Sempere et al. 2004; Makeyev et al. 2007; Le et al. 2009). Our studies using PC12 and SH-SY5Y cells as a cellular model of neuronal differentiation have identified upregulation in the expression of 22 miRNAs in nerve growth factor (NGF)-differentiated PC12 cells, while in RA+ brain-derived neurotrophic factor (BDNF)-differentiated SH-SY5Y cells, 77 miRNAs were upregulated and 17 miRNAs were downregulated after differentiation (Pandey et al. 2015b; Jauhari et al. 2017).

Schratt et al. (2006) were the first to identify the role of miRNAs (miR-134) in spine development of dendrites (Schratt et al. 2006). The brain is identified as one of the miRNA-enriched organs (Kloosterman et al. 2006; Wienholds et al. 2003; Wienholds and Plasterk 2005; Krichevsky et al. 2003, 2006; Gao 2008).

Evidence from Dicer Knockout Studies

Dicer is an enzyme, which plays a central role in miRNA maturation and loading of miRNAs on target mRNA molecules (Jiang et al. 2005; Cifuentes et al. 2010). Knockout studies of Dicer gene have shown that expression of Dicer is necessary for development, as dicer knockout animals were not viable (Gonzalez and Behringer 2009; Sayed and Abdellatif 2011). Studies using brain-specific Dicer knockout animals have observed several defects and abnormality in brain development in different brain regions (cerebellum, midbrain, cortex, and hippocampus) and neural crest as well as in dopaminergic cells differentiation (Huang et al. 2010; Cheng et al. 2014; Davis et al. 2008; Bernstein et al. 2003). Conditional Dicer knockout mice has shown a reduction in forebrain size with an increased rate of apoptosis in differentiating neurons (Makeyev et al. 2007). In contrast, the NSCs in which Dicer was deleted can self-renew but show enlarged nuclei, with the abnormal differentiation and apoptosis at mitogens withdrawn, suggesting a role of Dicer in survival and differentiation of NSCs (Kawase-Koga et al. 2010). Furthermore, Dicer deletion in the hippocampal and cortical region of brain has shown to induce microcephaly with decreased number of dendrites (Davis et al. 2008). However, as Dicer is responsible for the processing of small ncRNAs like short-interfering RNAs (siRNAs) and miRNAs, the defects which were observed in Dicer knockout models in vitro and in vivo could be due to defects in biogenesis of siRNAs and/or miRNAs. Direct evidence for elementary role of miRNAs in the brain development became noticeable when neural tube morphological defects and abnormal neuronal differentiation were observed in Dicer-deleted zebrafish, which were rescued by enforced expression of miR-430 (Giraldez et al. 2005). The level of mature miRNAs is maintained and managed by various mechanisms of transcriptional regulation, enzymatic processing, and stability. Expression of miRNAs is regulated in a manner, which maintains distinct and specific expression patterns of mRNAs at specific time (Wienholds et al. 2005; Kloosterman et al. 2006; Wienholds et al. 2003), which is regulated dramatically with the change in stage and time of development like neuronal differentiation, neuronal proliferation, neuronal apoptosis (Gangaraju and Lin 2009) (Fig. 1). Interestingly, our previous studies also demonstrated the crucial role of Dicer in neuronal differentiation (Pandey et al. 2015b; Jauhari et al. 2017). Dicer knockdown induced cell senescence and neurite shortening in differentiating SH-SY5Y and PC12 cells (Jauhari et al. 2017; Pandey et al. 2015b).

Evidence Using Cellular Models

Availability of different cellular models like SH-SY5Y and IMR32 (human neuroblastomas), N2a (mouse neuroblastoma), PC12 (rat pheochromocytoma), and Neural Stem cells of neuronal differentiation provided excellent tool to study the molecular changes happening in brain during development (Azari and Reynolds 2016; Xie et al. 2010; Tremblay et al. 2010; Guroff 1985). Changes in the expression of miRNAs have been observed as cellular commitment proceeds in the developing brain and cells consistently, which shows a significant role of miRNAs in the regulation of cell-cycle progression (Krichevsky et al. 2003; Hohjoh and Fukushima 2007a, b). It has been reported by several studies that the miRNAs, which maintain the proliferative nature of NPCs, decrease with increasing commitment,

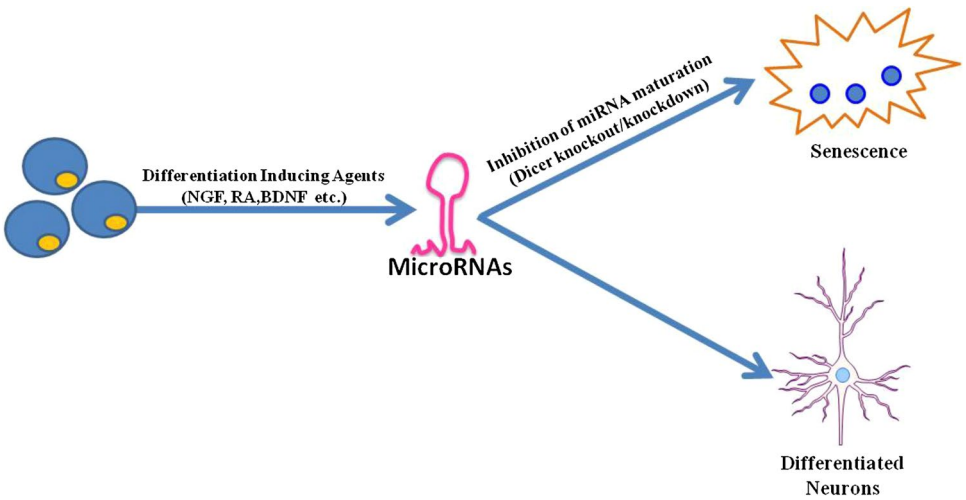

Fig. 1 Role of miRNAs in neuronal differentiation and development

while other miRNAs, which induce differentiation, increase as cells differentiate (Liu and Zhao 2009). miRNAs which are commonly upregulated in different systems reported by different studies are miR-124, miR-125b, miR-9, miR-145, miR-34, miR-200, miR-29, miR-221, and miR-222. Studies from our lab using PC12 cell as a model for neuronal differentiation have studied the expression of 754 miRNAs and identified the upregulation in expression of 22 miRNAs in PC12 cells differentiated by NGF (Pandey et al. 2015b). Moreover, our recently published study has also shown the crucial role of miR-29 and miR-145 in neuronal differentiation. Our studies demonstrated that level of miR-29 regulates the expression of miR-145 by P53 pathway, which regulates cell proliferation by inhibiting reprogramming transcription factors (SOX2, OCT4, KLF4, and NANOG) and induced differentiation in SH-SY5Y cells (Jauhari et al. 2018b).

Role of miRNA (miR-124) has also been reported in brain-specific splicing of pre-mRNA, which promotes neuronal differentiation. Brain-specific miR-124 targets PTBP1 directly, and regulates the alternative pre-mRNA splicing (Makeyev et al. 2007). During neuronal differentiation, miR-124 targets PTBP1 and reduces its expression, which leads to correctly spliced PTBP2 accumulation and its protein, resulting in increased neuronal differentiation (Makeyev et al. 2007). Yu et al. (2008) also demonstrated the role of miR-124 in neuronal differentiation, they reported that miR-124 induced neurite outgrowth in differentiating mouse cortical neurons. In addition, they also reported Cdc42 as a target of miR-124, which regulates sub-cellular localization of Rac1 (Yu et al. 2008). Several other studies have also shown the role of miR-124 in embryonic CNS development, adult neurogenesis, and neural tube development (Visvanathan et al. 2007; Cheng et al. 2009; Cao et al. 2007). Moreover, miR-124a has also been reported as a molecular indicator for the assessment of differentiation of neurons (Hohjoh and Fukushima 2007b). Hamada et al. (2012) carried out a microarray analysis in NGF-induced differentiated PC12 for miRNAs and reported alterations in the expression of 20 miRNAs. Out of 20 altered miRNAs, miR-221 was increased maximally, induced neuronal outgrowth, while inhibition of miR-221 attenuated NGF-mediated neuronal differentiation by downregulating the expression of Synapsin 1 (Hamada et al. 2012). Studies from our lab have also identified miR-221/222 as one of the three major miRNA families upregulated in NGF-induced differentiation of PC12 cells (Pandey et al. 2015b). Terasawa et al. (2009) reported BIM gene as a potential target for miR-221/222 during neuronal differentiation. Studies of Kawasaki and Taira (2003) revealed that miR-23 regulates retinoic acid-induced neuronal differentiation by regulating the expression of Hes1 in NT2 cells (Kawasaki and Taira 2003). Le et al. (2009) have reported that miR-125b targets and regulates the expression of multiple genes and induces neuronal differentiation in SH-SY5Y cells (Narendra et al. 2009). Moreover, miR-125b has also demonstrated to regulate neural stem/progenitor cell proliferation, differentiation, and migration (Cui et al. 2012). Regulation of miR-9 has been studied extensively in brain development and maturation. Growing pieces of evidence have suggested that miR-9 plays a crucial role in brain development. Sim et al. (2016) have demonstrated miR-9-3p as brain-enriched miRNA which regulates hippocampal synaptic plasticity, learning, and memory. In addition, it was also reported that miR-9 targets REST and regulates dendritic development and synaptic transmission in vivo (Giusti et al. 2014). Roese-Koerner et al. (2016) have demonstrated that miR-9/9* regulates neural stem cell self-renewal as well as differentiation by controlling Notch activity and targeting NOTCH2 and HES1 genes. Moreover, it has also been demonstrated that miR-9 and miR-124 target and regulate the expression of Rap2a synergistically to sustain homeostatic dendritic complexity during neuronal development and maturation (Xue et al. 2016). Moreover, it has been shown that ectopic over-expression of miR-9 significantly induced neuronal differentiation in mouse retinal neural stem cells by regulating the expression of PTBP1 (Qi 2015). Role of miR-9 in neuronal differentiation has also been reported by Zhang et al. (2015). Their studies have shown that miR-9 induces neural differentiation by regulating autophagy (Zhang et al. 2015). Along with these functions, miR-9 was also demonstrated as a switch between early-born motor neurons and late-born motor neurons population (Luxenhofer et al. 2014). All important miRNAs and their proposed functions are listed in Table 1.

Members of miR-34 (miR-34a, -b and miR-34c) and miR-200 families are extensively studied for their role in cell fate determination including neural cell development, stem cell proliferation/differentiation, and EMT. Both miR-34 and miR-200 families are multifunctional and are deregulated by several factors. Interestingly, their role has been identified as a switch between cell fate decisions like proliferation/differentiation; epithelial/mesenchymal; stem cells/specialized cells.

MiR-34 Family

In mammals, miR-34 family consists of three members, i.e., miR-34a, miR-34b, and miR-34c, which are transcribed from two separate transcripts (Hermeking 2010). In humans, miR-34a precursor is transcribed from chromosome 1. The precursors of miR-34b and miR-34c are co-transcribed from the same region of chromosome 11 (Hermeking 2010). Studies from our lab and elsewhere has shown that expression of miR-34 family is P53 dependent and stabilization of P53 proteins dramatically upregulates miR-34 (Jauhari et al. 2018b). In cancer development, the role of miR-34 family has been demonstrated in determining the fate of

Table 1 List of most potential miRNAs, their target genes, and proposed function in brain development

miRNA	Target genes	Proposed function	References
miR-124	PTBP1, Cdc42, REST, SOX9, LAMC1, CD29	Neuronal differentiation, neurite outgrowth, embryonic CNS development, adult neurogenesis, neural tube development	Makeyev et al. (2007), Yu et al. (2008), Visvanathan et al. (2007), Cheng et al. (2009), Cao et al. (2007)
miR-221/222	SYN1, BIM	Neuronal outgrowth, neuronal differentiation, cell-cycle regulation	Hamada et al. (2012), Terasawa et al. (2009)
miR-125b	Musashi1, Nestin	Neuronal differentiation, neural stem/progenitor cell proliferation/differentiation, and migration	Narendra et al. (2009), Gioia et al. (2014), Cui et al. (2012)
miR-9	NOTCH2, HES1, Rap2a, PTBP1, REST	Hippocampal synaptic plasticity, learning and memory, neural stem cell self-renewal and differentiation, maintains homeostatic dendritic complexity along with neuronal development and maturation, neuronal differentiation of mouse retinal stem cells, dendritic development, dendritic growth, and synaptic transmission	Sim et al. (2016), Roese-Koerner et al. (2016), Xue et al. (2016), Qi (2015), Zhang et al. (2015), Giusti et al. (2014)
miR-34 family	SIRT1, Dll1, SYT1, STX1a	Neural stem cell differentiation, neurite elongation, neuronal differentiation, regulation of cell proliferation, synaptogenesis	Aranha et al. (2011), de Antonellis et al. (2011), Agostini et al. (2011)
miR-200 family	SOX2, OCT4, ZEB1, E2F3, GATA4	Induced neuronal differentiation and inhibits proliferation, neurite formation, cell-cycle exit and differentiation, olfactory neurogenesis, neural induction	Pandey et al. (2015b), Peng et al. (2012), Santra et al. (2016), Choi et al. (2008)
miR-29 family	BH3, VDAC1, ICAT	Neurogenesis, neuronal maturation, neuronal survival	Kole et al. (2011), Roshan et al. (2014), Shin et al. (2014)

cells between three stages, i.e., epithelial, mesenchymal, or hybrid of epithelial and mesenchymal (Lu et al. 2013). Determination of cell fate between the above three phenotypes is, in fact, regulated by two closely interconnected chimeric modules—the miR-34/SNAIL and the miR-200/ZEB mutual-inhibition feedback circuits (Lu et al. 2013). Studies have shown that members of the miR-34 family inhibit cell-cycle progression by enforcing cells towards cell-cycle exit, which results in the generation of mature and differentiated cells (Otto et al. 2017). Recent studies by Choi et al. (2017) have demonstrated the role of miR-34a in restricting the cell fate potential of ESCs and iPSCs to a pluripotent state from bipotential stem cells, which can convert into both embryonic and extraembryonic lineage. Diminished expression of miR-34 family observed in different types of cancer has promoted researchers to use the mimics of miR-34 as a potential therapy for cancers and studies have reached to clinical trial stages (Hosseinahli et al. 2018). Recently, it has been shown that miR-34c-5p selectively targets RAB27b and promotes the eradication of acute myeloid leukemia stem cells by inducing senescence (Peng et al. 2018). Studies of Otto et al. 2017 have shown that miR-34/449 plays an essential and rate-limiting role in downregulating the expression of cell-cycle proteins and enforces cell-cycle exit during epithelial cell differentiation. Siemens et al. (2011) have demonstrated that the frequent inactivation of miR-34a/b/c or p53 and/or in cancerous cells, shifts the equilibrium of these reciprocal regulations towards the mesenchymal state and halts cells in a metastatic state. Members of miR-34 family are negative regulators of cell proliferation and but potential suppressors of tumorigenesis. Members of miR-34 family target multiple proteins of the cell-cycle machinery including cyclin D1, cyclin E2, CDK4, CDK6, CDC25A, and E2F3 and trigger cell-cycle arrest (mainly during G1 phase) and apoptosis. In human cancers, members of miR-34 family are frequently downregulated, which suggests a potential role of this miRNA family in tumor suppression (Hermeking 2010). Expression of miR-34 along with P53 and p21 proteins, collectively suppresses the somatic reprogramming via multiple pathways and acts as a barrier in somatic cell reprogramming (Choi et al. 2011). Interestingly, unlike P53, deletion of which enhances reprogramming at the expense of iPSC pluripotency, miR-34a knockout also induces iPSC generation without compromising self-renewal and differentiation processes (Choi et al. 2011). MiR-34a possibly acts by repression of pluripotency genes, like *Nanog, Sox2*, and *Mycn* (*N-Myc*) (Choi et al. 2011). Zou et al. (2017) have reported that miR-34a is inhibited in human osteosarcoma stem-like cells and promotes invasion, tumorigenic ability, and self-renewal capacity.

Role of miR-34 family has also been studied extensively in neurodevelopment and neuronal apoptosis using different cellular neuronal models. Our unbiased profiling studies have identified miR-34 family as one of the three most upregulated miRNAs in PC12 cells differentiated with NGF (Pandey et al. 2015b). Further, we have identified P53 as a mediator of nerve growth factor (NGF)-induced miR-34a expression, which arrests cell-cycle progression in G1 Phase in differentiating PC12 cells (Jauhari et al. 2018a). Interestingly, our studies have also revealed that increased expression of miR-34a controls the P53 level in differentiated PC12 cells in feedback inhibition manner, which probably prevents differentiated cells from P53-induced apoptosis (Jauhari et al. 2018a). During neural cell differentiation coordinated expression of miR-34 and P53 helps to differentiate PC12 cells and maintain its differentiated status. Aranha et al. (2011) has also shown an involvement of miR-34a in the regulation of mouse NSC differentiation. Over-expression of miR-34a increased postmitotic neurons and neurite elongation in mouse NSCs, whereas diminishing miR-34a expression had inhibited differentiation of neurons (Aranha et al. 2011). In differentiating neurons, SIRT1 gene has been identified as a target of miR-34a (Aranha et al. 2011). de Antonellis et al. (2011) have found out that miR-34a regulates neuronal differentiation by targeting Notch ligand Delta-like 1 (Dll1) gene. Increased expression of miR-34a negatively regulates cell proliferation by inhibiting the expression of Dll1 (de Antonellis et al. 2011). Agostini et al. (2011) reported the crucial role of miR-34a in neuronal differentiation of neuroblastoma cells as well as cortical neurons. TAp73 was identified as transcription factor, which exclusively regulates the expression of miR-34a among the miR-34 family. Synaptotagmin-1 and Syntaxin-1a were also identified as potential targets for miR-34a, which regulate synaptogenesis in developing neurons. Liu et al. (2012) has demonstrated that miR-34 modulates aging and neurodegeneration in Drosophila. Overall, it seems that along with playing multiple roles in cellular physiology, members of miR-34 family regulate somatic reprogramming and neural differentiation, when they are regulated by levels of P53 proteins (Choi et al. 2011; Jauhari et al. 2018a, b). More interesting is the feedback loop formation between the expression of miR-34 and levels of P53 proteins, especially during neural development (Jauhari et al. 2018a; Yang et al. 2018).

MiR-200 Family

Similar to miR-34 family, members of miR-200 family are also highly conserved throughout deuterostome and across all classes of vertebrates, including fish, amphibians, reptiles, birds, and mammals (Wheeler et al. 2009). The miR-200 family composed of five mature miRNAs: miR-200a, miR-200b, miR-200c, miR-141, and miR-429, which are expressed as two separate polycistronic pri-miRNA transcripts, miR-200b-200a-429 and miR-200c-141, located on human chromosomes 1 and 12, respectively. Among

the miR-220 family, miR-200a, -200b, and -200c are more extensively studied (Humphries and Yang 2015). It has been observed in various studies that miR-200 family regulates cell proliferation, cell differentiation, cell transition, neurogenesis, and neuronal differentiation (Pandey et al. 2015b; Burk et al. 2008; Choi et al. 2008). Pluripotency is controlled by a complex regulatory network, which includes several transcription factors, chromatin-modifying enzymes, and post-transcriptional regulators like miRNAs. The core transcriptional network required for pluripotency comprises OCT4, NANOG, and SOX3 proteins. Levels of pluripotency-regulating transcription factor proteins are regulated by miRNAs like miR-200 family, miR-145, miR-302 (Wang et al. 2013). Among the different identified miRNAs, the role of miR-200 family is demonstrated most strongly in the regulation of pluripotency-regulating transcription factor proteins and cell fate determination like EMT, neural development, and stemness (Brabletz and Brabletz 2010).

Epithelial-to-mesenchymal transition (EMT) is a vital phenomenon in development and disease (Kalluri and Weinberg 2009). Zinc-finger enhancer binding (ZEB) proteins (ZEB1 and ZEB2) are known to play a fundamental role during EMT (Chua et al. 2007; Shin and Blenis 2010). Accumulating evidence suggests that miR-200 family is a critical regulator of ZEB proteins during development and disease (Brabletz and Brabletz 2010; Gregory et al. 2011). ZEB proteins and members of miR-200 family are reported that they are linked to each other in a feedback inhibition fashion (Brabletz and Brabletz 2010). ZEB proteins and miR-200 family members not only regulate EMT but are also known to involve in the regulation of stemness and differentiation; longevity and senescence; cell-cycle arrest and proliferation; cell survival and apoptosis (Brabletz and Brabletz 2010). Embryonic stem (ES) cells have been shown to express ZEB1 and regulate stemness, while reduced expression of ZEB1 is reported during their differentiation (Ben-Porath et al. 2008). Differentiation of ES-cell is associated with the increased expression of miR-200 family members (Bar et al. 2008; Wellner et al. 2009).

We revealed that miR-200 family plays a critical role in proliferation as well as differentiation of neurons. Our studies have shown that members of miR-200 family inhibit the proliferation of neurons by targeting SOX2 and OCT4 and induce the differentiation of PC12 cells (Pandey et al. 2015b). Elevated level of miR-200 family has also been reported during differentiation of neural stem cells (NSCs), which clearly demonstrate that miR-200 family has a direct role in neuronal differentiation. We identified that over-expression of miR-200 in PC12 cells induced neurite formation, whereas knockdown of miR-200 induced proliferation (Pandey et al. 2015b). Role of miR-200 has also been demonstrated in progenitor cell-cycle exit and differentiation by Peng et al. (2012). A unilateral negative feedback loop was identified between miR-200 and Sox2/E2F3, which regulate cell-cycle exit and neuronal differentiation of stem cells or neural progenitor cells (Peng et al. 2012). Choi et al. (2008) reported high olfactory enrichment of miR-200 family with a role in olfactory neurogenesis. In olfactory progenitor cells, loss of function of the miR-200 family phenocopies the terminal differentiation defect, as observed in the absence of all miRNA activity (Choi et al. 2008). Du et al. (2013) have demonstrated that miR-200 and miR-96 families coordinate to regulate neural induction, in which miR-200 family members repress neural differentiation by targeting ZEBs (ZEB1 and ZEB2) (Du et al. 2013). MiR-200b has also reported to regulate cell growth and differentiation by regulating the expression of GATA-4 and Cyclin D1 (Yao et al. 2013).

Recently, miR-200c has shown to regulate dopaminergic neurogenesis and migration by controlling Zeb2. Zeb2 is regulated by a negative feedback loop with miR-200c in embryonic ventral midbrain. Increased expression of Zeb2 reduces the CXCR4, NR4A2, and PITX3 level, resulting in migration and mDA differentiation defects in vivo. MiR-200c knockdown restores this phenotype suggesting Zeb2-miR-200c feedback loop prevents the premature neuronal differentiation and their migration (Yang et al. 2018).

Summary

Studies carried out in the last two decades have provided very strong evidence for the involvement of miRNAs in regulating the fate of the cells moving to maturation or proliferation of stem cells and maintenance of stemness/pluripotency. Role of miRNAs (miR-200 family, miR-34 family, miR-145) identified in regulating protein levels of SOX2/KLF4/OCT4/ZEB proteins added in our capabilities to generate iPSCs. In future, with the development of new technologies, enabling the management of expression of specific miRNAs in selected cells and tissues will be the biggest tool against the complex diseases. In conclusion, expression of miR-34 plays a significant role in both neural development and maintenance of mature and differentiated neurons (Fig. 2).

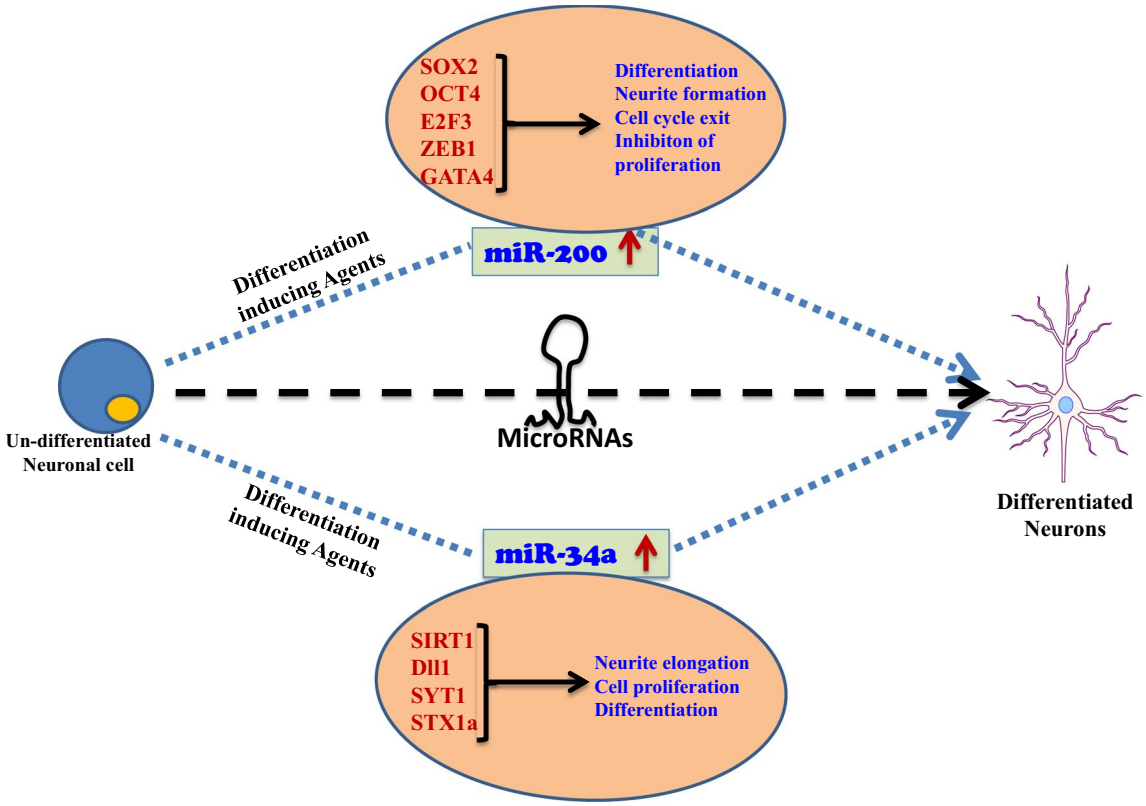

Fig. 2 Schematic representation of miR-200 and miR34 family in shaping of developing brain

Acknowledgements Funding for the work carried out in the present study has been provided by CSIR network projects (Grant Nos. BSC0111, BSC0115). Mr. Abhishek Jauhari is grateful to UGC, New Delhi, for providing research fellowship. The CSIR-IITR communication reference number is 3426.

Compliance with Ethical Standards

Conflict of interest There is no conflict of interest regarding the publication of this review article.

References

Aberdam, D., Candi, E., Knight, R. A., & Melino, G. (2008). miRNAs, 'stemness' and skin. *Trends in Biochemical Sciences, 33*(12), 583–591.

Agostini, M., Tucci, P., Killick, R., Candi, E., Sayan, B. S., di val Cervo, P. R., et al. (2011). Neuronal differentiation by TAp73 is mediated by microRNA-34a regulation of synaptic protein targets. *Proceedings of the National Academy of Sciences, 108*(52), 21093–21098.

Alvarez-Garcia, I., & Miska, E. A. (2005). MicroRNA functions in animal development and human disease. *Development, 132*(21), 4653–4662.

Amaral, P. P., & Mattick, J. S. (2008). Noncoding RNA in development. *Mammalian Genome, 19*(7–8), 454–492.

Ambros, V., Bartel, B., Bartel, D. P., Burge, C. B., Carrington, J. C., Chen, X., et al. (2003). A uniform system for microRNA annotation. *RNA, 9*(3), 277–279.

Andersen, S. L. (2003). Trajectories of brain development: point of vulnerability or window of opportunity? *Neuroscience and Biobehavioral Reviews, 27*(1), 3–18.

Aranha, M. M., Santos, D. M., Solá, S., Steer, C. J., & Rodrigues, C. (2011). miR-34a regulates mouse neural stem cell differentiation. *PLoS ONE, 6*(8), e21396.

Axtell, M. J., & Bartel, D. P. (2005). Antiquity of microRNAs and their targets in land plants. *The Plant Cell, 17*(6), 1658–1673.

Azari, H., & Reynolds, B. A. (2016). In vitro models for neurogenesis. *Cold Spring Harbor Perspectives in Biology, 8*(6), a021279.

Bartel, D. P. (2004). MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell, 116*(2), 281–297.

Bernstein, E., Kim, S. Y., Carmell, M. A., Murchison, E. P., Alcorn, H., Li, M. Z., et al. (2003). Dicer is essential for mouse development. *Nature Genetics, 35*(3), 215–217.

Bhaskaran, M., & Mohan, M. (2014). MicroRNAs: History, biogenesis, and their evolving role in animal development and disease. *Veterinary Pathology, 51*(4), 759–774.

Brabletz, S., & Brabletz, T. (2010). The ZEB/miR-200 feedback loop—A motor of cellular plasticity in development and cancer? *EMBO Reports, 11*(9), 670–677.

Brennecke, J., Hipfner, D. R., Stark, A., Russell, R. B., & Cohen, S. M. (2003). Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. *Cell, 113*(1), 25–36.

Burk, U., Schubert, J., Wellner, U., Schmalhofer, O., Vincan, E., Spaderna, S., et al. (2008). A reciprocal repression between

ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Reports, 9*(6), 582–589.
Burmistrova, O., Goltsov, A., Abramova, L., Kaleda, V., Orlova, V., & Rogaev, E. (2007). MicroRNA in schizophrenia: genetic and expression analysis of miR-130b (22q11). *Biochemistry (Moscow), 72*(5), 578–582.
Cao, X., Pfaff, S. L., & Gage, F. H. (2007). A functional study of miR-124 in the developing neural tube. *Genes & Development, 21*(5), 531–536.
Carleton, M., Cleary, M. A., & Linsley, P. S. (2007). MicroRNAs and cell cycle regulation. *Cell Cycle, 6*(17), 2127–2132.
Chen, F., & Hu, S. J. (2012). Effect of microRNA-34a in cell cycle, differentiation, and apoptosis: A review. *Journal of Biochemical and Molecular Toxicology, 26*(2), 79–86.
Chen, K., & Rajewsky, N. (2007). The evolution of gene regulation by transcription factors and microRNAs. *Nature Reviews Genetics, 8*(2), 93–103.
Cheng, L.-C., Pastrana, E., Tavazoie, M., & Doetsch, F. (2009). miR-124 regulates adult neurogenesis in the subventricular zone stem cell niche. *Nature Neuroscience, 12*(4), 399–408.
Cheng, S., Zhang, C., Xu, C., Wang, L., Zou, X., & Chen, G. (2014). Age-dependent neuron loss is associated with impaired adult neurogenesis in forebrain neuron-specific Dicer conditional knockout mice. *The international journal of biochemistry & cell biology, 57,* 186–196.
Chinwalla, A. T., Cook, L. L., Delehaunty, K. D., Fewell, G. A., Fulton, L. A., Fulton, R. S., et al. (2002). Initial sequencing and comparative analysis of the mouse genome. *Nature, 420*(6915), 520–562.
Choi, Y. J., Lin, C.-P., Ho, J. J., He, X., Okada, N., Bu, P., et al. (2011). miR-34 miRNAs provide a barrier for somatic cell reprogramming. *Nature Cell Biology, 13*(11), 1353.
Choi, Y. J., Lin, C.-P., Risso, D., Chen, S., Tan, M. H., Li, J. B., et al. (2017). Deficiency of microRNA miR-34a expands cell fate potential in pluripotent stem cells. *Science, 355*(6325). https://doi.org/10.1126/science.aag1927.
Choi, P. S., Zakhary, L., Choi, W.-Y., Caron, S., Alvarez-Saavedra, E., Miska, E. A., et al. (2008). Members of the miRNA-200 family regulate olfactory neurogenesis. *Neuron, 57*(1), 41–55.
Chua, H., Bhat-Nakshatri, P., Clare, S., Morimiya, A., Badve, S., & Nakshatri, H. (2007). NF-κB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: potential involvement of ZEB-1 and ZEB-2. *Oncogene, 26*(5), 711.
Cifuentes, D., Xue, H., Taylor, D. W., Patnode, H., Mishima, Y., Cheloufi, S., et al. (2010). A novel miRNA processing pathway independent of Dicer requires Argonaute2 catalytic activity. *Science, 328*(5986), 1694–1698.
Colantuoni, C., Lipska, B. K., Ye, T., Hyde, T. M., Tao, R., Leek, J. T., et al. (2011). Temporal dynamics and genetic control of transcription in the human prefrontal cortex. *Nature, 478*(7370), 519–523.
Coolen, M., & Bally-Cuif, L. (2009). MicroRNAs in brain development and physiology. *Current Opinion in Neurobiology, 19*(5), 461–470.
Cui, Y., Xiao, Z., Han, J., Sun, J., Ding, W., Zhao, Y., et al. (2012). MiR-125b orchestrates cell proliferation, differentiation and migration in neural stem/progenitor cells by targeting Nestin. *BMC Neuroscience, 13*(1), 1.
Datson, N. A., van der Perk, J., de Kloet, E. R., & Vreugdenhil, E. (2001). Expression profile of 30,000 genes in rat hippocampus using SAGE. *Hippocampus, 11*(4), 430–444.
Davis, T. H., Cuellar, T. L., Koch, S. M., Barker, A. J., Harfe, B. D., McManus, M. T., et al. (2008). Conditional loss of Dicer disrupts cellular and tissue morphogenesis in the cortex and hippocampus. *The Journal of Neuroscience, 28*(17), 4322–4330.
de Antonellis, P., Medaglia, C., Cusanelli, E., Andolfo, I., Liguori, L., De Vita, G., et al. (2011). MiR-34a targeting of Notch ligand delta-like 1 impairs CD15/CD133 tumor-propagating cells and supports neural differentiation in medulloblastoma. *PLoS ONE, 6*(9), e24584.
Du, Z.-W., Ma, L.-X., Phillips, C., & Zhang, S.-C. (2013). miR-200 and miR-96 families repress neural induction from human embryonic stem cells. *Development, 140*(12), 2611–2618.
Friedman, R. C., Farh, K. K.-H., Burge, C. B., & Bartel, D. P. (2009). Most mammalian mRNAs are conserved targets of microRNAs. *Genome Research, 19*(1), 92–105.
Gangaraju, V. K., & Lin, H. (2009). MicroRNAs: Key regulators of stem cells. *Nature Reviews Molecular Cell Biology, 10*(2), 116.
Gao, F.-B. (2008). Posttranscriptional control of neuronal development by microRNA networks. *Trends in Neurosciences, 31*(1), 20–26.
Gioia, U., Di Carlo, V., Caramanica, P., Toselli, C., Cinquino, A., Marchioni, M., et al. (2014). Mir-23a and mir-125b regulate neural stem/progenitor cell proliferation by targeting Musashi1. *RNA Biology, 11*(9), 1105–1112.
Giraldez, A. J., Cinalli, R. M., Glasner, M. E., Enright, A. J., Thomson, J. M., Baskerville, S., et al. (2005). MicroRNAs regulate brain morphogenesis in zebrafish. *Science, 308*(5723), 833–838.
Giusti, S. A., Vogl, A. M., Brockmann, M. M., Vercelli, C. A., Rein, M. L., Trümbach, D., et al. (2014). MicroRNA-9 controls dendritic development by targeting REST. *Elife, 3,* e02755.
Gonzalez, G., & Behringer, R. R. (2009). Dicer is required for female reproductive tract development and fertility in the mouse. *Molecular Reproduction and Development, 76*(7), 678–688.
Gregory, P. A., Bracken, C. P., Bert, A. G., & Goodall, G. J. (2008). MicroRNAs as regulators of epithelial-mesenchymal transition. *Cell Cycle, 7*(20), 3112–3117.
Gregory, P. A., Bracken, C. P., Smith, E., Bert, A. G., Wright, J. A., Roslan, S., et al. (2011). An autocrine TGF-β/ZEB/miR-200 signaling network regulates establishment and maintenance of epithelial-mesenchymal transition. *Molecular Biology of the Cell, 22*(10), 1686–1698.
Guroff, G. (1985). PC12 cells as a model of neuronal differentiation. In J. E. Bottenstein & G. Sato (Eds.), *Cell culture in the neurosciences* (pp. 245–272). Boston: Springer.
Gustincich, S., Sandelin, A., Plessy, C., Katayama, S., Simone, R., Lazarevic, D., et al. (2006). The complexity of the mammalian transcriptome. *The Journal of Physiology, 575*(2), 321–332.
Hamada, N., Fujita, Y., Kojima, T., Kitamoto, A., Akao, Y., Nozawa, Y., et al. (2012). MicroRNA expression profiling of NGF-treated PC12 cells revealed a critical role for miR-221 in neuronal differentiation. *Neurochemistry International, 60*(8), 743–750.
He, X., & Rosenfeld, M. G. (1991). Mechanisms of complex transcriptional regulation: implications for brain development. *Neuron, 7*(2), 183–196.
Hermeking, H. (2010). The miR-34 family in cancer and apoptosis. *Cell Death and Differentiation, 17*(2), 193–199.
Hohjoh, H., & Fukushima, T. (2007a). Expression profile analysis of microRNA (miRNA) in mouse central nervous system using a new miRNA detection system that examines hybridization signals at every step of washing. *Gene, 391*(1), 39–44.
Hohjoh, H., & Fukushima, T. (2007b). Marked change in microRNA expression during neuronal differentiation of human teratocarcinoma NTera2D1 and mouse embryonal carcinoma P19 cells. *Biochemical and Biophysical Research Communications, 362*(2), 360–367.
Hosseinahli, N., Aghapour, M., Duijf, P. H., & Baradaran, B. (2018). Treating cancer with microRNA replacement therapy: A literature review. *Journal of cellular Physiology, 233,* 5574–5588.
Huang, T., Liu, Y., Huang, M., Zhao, X., & Cheng, L. (2010). Wnt1-cre-mediated conditional loss of Dicer results in malformation of the midbrain and cerebellum and failure of neural crest and

dopaminergic differentiation in mice. *Journal of Molecular Cell Biology, 2*(3), 152–163.
Huang, B., & Zhang, R. (2014). Regulatory non-coding RNAs: revolutionizing the RNA world. *Molecular Biology Reports, 41*(6), 3915–3923.
Humphries, B., & Yang, C. (2015). The microRNA-200 family: Small molecules with novel roles in cancer development, progression and therapy. *Oncotarget, 6*(9), 6472–6498.
Hwang, H., & Mendell, J. (2006). MicroRNAs in cell proliferation, cell death, and tumorigenesis. *British Journal of Cancer, 94*(6), 776.
Ivey, K. N., Muth, A., Arnold, J., King, F. W., Yeh, R.-F., Fish, J. E., et al. (2008). MicroRNA regulation of cell lineages in mouse and human embryonic stem cells. *Cell Stem Cell, 2*(3), 219–229.
Jauhari, A., Singh, T., Pandey, A., Singh, P., Singh, N., Srivastava, A. K., et al. (2017). Differentiation induces dramatic changes in miRNA profile, where loss of dicer diverts differentiating SH-SY5Y cells toward senescence. *Molecular Neurobiology, 54*(7), 4986–4995.
Jauhari, A., Singh, T., Singh, P., Parmar, D., & Yadav, S. (2018a). Regulation of miR-34 family in neuronal development. *Molecular Neurobiology, 55*(2), 936–945.
Jauhari, A., Singh, T., & Yadav, S. (2018b). Expression of miR-145 and its target proteins are regulated by miR-29b in differentiated neurons. *Molecular Neurobiology*. https://doi.org/10.1007/s12035-018-1009-9.
Jiang, F., Ye, X., Liu, X., Fincher, L., McKearin, D., & Liu, Q. (2005). Dicer-1 and R3D1-L catalyze microRNA maturation in Drosophila. *Genes & Development, 19*(14), 1674–1679.
Kalluri, R., & Weinberg, R. A. (2009). The basics of epithelial-mesenchymal transition. *The Journal of Clinical Investigation, 119*(6), 1420–1428.
Kang, H. J., Kawasawa, Y. I., Cheng, F., Zhu, Y., Xu, X., Li, M., et al. (2011). Spatio-temporal transcriptome of the human brain. *Nature, 478*(7370), 483–489.
Kapranov, P., St Laurent, G., Raz, T., Ozsolak, F., Reynolds, C. P., Sorensen, P. H., et al. (2010). The majority of total nuclear-encoded non-ribosomal RNA in a human cell is' dark matter'un-annotated RNA. *BMC Biology, 8*(1), 149.
Karp, X., & Ambros, V. (2005). Encountering microRNAs in cell fate signaling. *Science, 310*(5752), 1288–1289.
Kawasaki, H., & Taira, K. (2003). Hes1 is a target of microRNA-23 during retinoic-acid-induced neuronal differentiation of NT2 cells. *Nature, 423*(6942), 838–842.
Kawase-Koga, Y., Low, R., Otaegi, G., Pollock, A., Deng, H., Eisenhaber, F., et al. (2010). RNAase-III enzyme Dicer maintains signaling pathways for differentiation and survival in mouse cortical neural stem cells. *Journal of Cell Science, 123*(4), 586–594.
Kawase-Koga, Y., Otaegi, G., & Sun, T. (2009). Different timings of Dicer deletion affect neurogenesis and gliogenesis in the developing mouse central nervous system. *Developmental Dynamics, 238*(11), 2800–2812.
Kiecker, C., & Lumsden, A. (2005). Compartments and their boundaries in vertebrate brain development. *Nature Reviews Neuroscience, 6*(7), 553.
Kim, V. N. (2005). MicroRNA biogenesis: Coordinated cropping and dicing. *Nature Reviews Molecular Cell Biology, 6*(5), 376–385.
Kloosterman, W. P., Wienholds, E., de Bruijn, E., Kauppinen, S., & Plasterk, R. H. (2006). In situ detection of miRNAs in animal embryos using LNA-modified oligonucleotide probes. *Nature Methods, 3*(1), 27–29.
Kole, A. J., Swahari, V., Hammond, S. M., & Deshmukh, M. (2011). miR-29b is activated during neuronal maturation and targets BH3-only genes to restrict apoptosis. *Genes & Development, 25*(2), 125–130.
Krek, A., Grün, D., Poy, M. N., Wolf, R., Rosenberg, L., Epstein, E. J., et al. (2005). Combinatorial microRNA target predictions. *Nature Genetics, 37*(5), 495–500.
Krichevsky, A. M., King, K. S., Donahue, C. P., Khrapko, K., & Kosik, K. S. (2003). A microRNA array reveals extensive regulation of microRNAs during brain development. *RNA, 9*(10), 1274–1281.
Krichevsky, A. M., Sonntag, K. C., Isacson, O., & Kosik, K. S. (2006). Specific microRNAs modulate embryonic stem cell–derived neurogenesis. *Stem Cells, 24*(4), 857–864.
Le, M. T., Xie, H., Zhou, B., Chia, P. H., Rizk, P., Um, M., et al. (2009). MicroRNA-125b promotes neuronal differentiation in human cells by repressing multiple targets. *Molecular and Cellular Biology, 29*(19), 5290–5305.
Lee, R. C., Feinbaum, R. L., & Ambros, V. (1993). The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell, 75*(5), 843–854.
Liu, N., Landreh, M., Cao, K., Abe, M., Hendriks, G.-J., Kennerdell, J. R., et al. (2012). The microRNA miR-34 modulates ageing and neurodegeneration in Drosophila. *Nature, 482*(7386), 519–523.
Liu, C., & Zhao, X. (2009). MicroRNAs in adult and embryonic neurogenesis. *NeuroMolecular Medicine, 11*(3), 141–152.
Loring, J., Wen, X., Lee, J., Seilhamer, J., & Somogyi, R. (2001). A gene expression profile of Alzheimer's disease. *DNA and Cell Biology, 20*(11), 683–695.
Lu, M., Jolly, M. K., Levine, H., Onuchic, J. N., & Ben-Jacob, E. (2013). MicroRNA-based regulation of epithelial–hybrid–mesenchymal fate determination. *Proceedings of the National Academy of Sciences, 110*(45), 18144–18149.
Lukiw, W. J. (2013). Circular RNA (circRNA) in Alzheimer's disease (AD). *Frontiers in Genetics, 4,* 307.
Luxenhofer, G., Helmbrecht, M. S., Langhoff, J., Giusti, S. A., Refojo, D., & Huber, A. B. (2014). MicroRNA-9 promotes the switch from early-born to late-born motor neuron populations by regulating Onecut transcription factor expression. *Developmental Biology, 386*(2), 358–370.
Makeyev, E. V., Zhang, J., Carrasco, M. A., & Maniatis, T. (2007). The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. *Molecular Cell, 27*(3), 435–448.
Mattick, J. S. (2001). Non-coding RNAs: The architects of eukaryotic complexity. *EMBO Reports, 2*(11), 986–991.
Mattick, J. S., & Makunin, I. V. (2006). Non-coding RNA. *Human Molecular Genetics, 15*((suppl_1)), R17–R29.
Miyoshi, N., Ishii, H., Nagano, H., Haraguchi, N., Dewi, D. L., Kano, Y., et al. (2011). Reprogramming of mouse and human cells to pluripotency using mature microRNAs. *Cell Stem Cell, 8*(6), 633–638.
Motti, D., Bixby, J. L., & Lemmon, V. P. (2012). MicroRNAs and neuronal development. *Seminars in Fetal and Neonatal Medicine, 17*(6), 347–352.
Muljo, S. A., Kanellopoulou, C., & Aravind, L. (2010). MicroRNA targeting in mammalian genomes: genes and mechanisms. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2*(2), 148–161.
Narendra, D., Tanaka, A., Suen, D.-F., & Youle, R. J. (2009). Parkin-induced mitophagy in the pathogenesis of Parkinson disease. *Autophagy, 5*(5), 706–708.
O'Donnell, K. A., Wentzel, E. A., Zeller, K. I., Dang, C. V., & Mendell, J. T. (2005). c-Myc-regulated microRNAs modulate E2F1 expression. *Nature, 435*(7043), 839–843.
Otto, T., Candido, S. V., Pilarz, M. S., Sicinska, E., Bronson, R. T., Bowden, M., et al. (2017). Cell cycle-targeting microRNAs promote differentiation by enforcing cell-cycle exit. *Proceedings of the National Academy of Sciences, 114*(40), 10660–10665.

Pandey, A., Jauhari, A., Singh, T., Singh, P., Singh, N., Srivastava, A. K., et al. (2015a). Transactivation of P53 by cypermethrin induced miR-200 and apoptosis in neuronal cells. *Toxicology Research, 4*(6), 1578–1586.

Pandey, A., Singh, P., Jauhari, A., Singh, T., Khan, F., Pant, A. B., et al. (2015b). Critical role of the miR-200 family in regulating differentiation and proliferation of neurons. *Journal of Neurochemistry, 133*(5), 640–652.

Peng, C., Li, N., Ng, Y.-K., Zhang, J., Meier, F., Theis, F. J., et al. (2012). A unilateral negative feedback loop between miR-200 microRNAs and Sox2/E2F3 controls neural progenitor cell-cycle exit and differentiation. *The Journal of Neuroscience, 32*(38), 13292–13308.

Peng, D., Wang, H., Li, L., Ma, X., Chen, Y., Zhou, H., et al. (2018). miR-34c-5p promotes eradication of acute myeloid leukemia stem cells by inducing senescence through selective RAB27B targeting to inhibit exosome shedding. *Leukemia, 32,* 1180.

Petri, R., Malmevik, J., Fasching, L., Åkerblom, M., & Jakobsson, J. (2014). miRNAs in brain development. *Experimental Cell Research, 321*(1), 84–89.

Qi, X. (2015). The role of miR-9 during neuron differentiation of mouse retinal stem cells. *Artificial Cells, Nanomedicine, and Biotechnology*. https://doi.org/10.3109/21691401.2015.1111231.

Rajewsky, N. (2006). microRNA target predictions in animals. *Nature Genetics, 38,* S8–S13.

Roese-Koerner, B., Stappert, L., Berger, T., Braun, N. C., Veltel, M., Jungverdorben, J., et al. (2016). Reciprocal regulation between bifunctional miR-9/9* and its transcriptional modulator notch in human neural stem cell self-renewal and differentiation. *Stem Cell Reports, 7*(2), 207–219.

Roshan, R., Shridhar, S., Sarangdhar, M. A., Banik, A., Chawla, M., Garg, M., et al. (2014). Brain-specific knockdown of miR-29 results in neuronal cell death and ataxia in mice. *RNA, 20*(8), 1287–1297.

Sandberg, R., Yasuda, R., Pankratz, D. G., Carter, T. A., Del Rio, J. A., Wodicka, L., et al. (2000). Regional and strain-specific gene expression mapping in the adult mouse brain. *Proceedings of the National Academy of Sciences, 97*(20), 11038–11043.

Santra, M., Chopp, M., Santra, S., Nallani, A., Vyas, S., Zhang, Z. G., et al. (2016). Thymosin beta 4 up-regulates miR-200a expression and induces differentiation and survival of rat brain progenitor cells. *Journal of Neurochemistry, 136*(1), 118–132.

Sayed, D., & Abdellatif, M. (2011). MicroRNAs in development and disease. *Physiological Reviews, 91*(3), 827–887.

Schratt, G. M., Tuebing, F., Nigh, E. A., Kane, C. G., Sabatini, M. E., Kiebler, M., et al. (2006). A brain-specific microRNA regulates dendritic spine development. *Nature, 439*(7074), 283–289.

Sempere, L. F., Freemantle, S., Pitha-Rowe, I., Moss, E., Dmitrovsky, E., & Ambros, V. (2004). Expression profiling of mammalian microRNAs uncovers a subset of brain-expressed microRNAs with possible roles in murine and human neuronal differentiation. *Genome Biology, 5*(3), R13.

Shin, S., & Blenis, J. (2010). *ERK2/Fra1/ZEB pathway induces epithelial-to-mesenchymal transition*. Routledge: Taylor & Francis.

Shin, J., Shin, Y., Oh, S., Yang, H., Yu, W., Lee, J., et al. (2014). MiR-29b controls fetal mouse neurogenesis by regulating ICAT-mediated Wnt/β-catenin signaling. *Cell Death & Disease, 5*(10), e1473.

Siemens, H., Jackstadt, R., Hünten, S., Kaller, M., Menssen, A., Götz, U., et al. (2011). miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. *Cell Cycle, 10*(24), 4256–4271.

Sim, S.-E., Lim, C.-S., Kim, J.-I., Seo, D., Chun, H., Yu, N.-K., et al. (2016). The brain-enriched MicroRNA miR-9-3p regulates synaptic plasticity and memory. *The Journal of Neuroscience, 36*(33), 8641–8652.

Singh, T., Jauhari, A., Pandey, A., Singh, P., B Pant, A., Parmar, D., et al. (2014). Regulatory triangle of neurodegeneration, adult neurogenesis and microRNAs. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 13*(1), 96–103.

Stefani, G., & Slack, F. J. (2008). Small non-coding RNAs in animal development. *Nature Reviews Molecular Cell Biology, 9*(3), 219.

Tanzer, A., & Stadler, P. F. (2004). Molecular evolution of a microRNA cluster. *Journal of Molecular Biology, 339*(2), 327–335.

Tau, G. Z., & Peterson, B. S. (2010). Normal development of brain circuits. *Neuropsychopharmacology, 35*(1), 147.

Terasawa, K., Ichimura, A., Sato, F., Shimizu, K., & Tsujimoto, G. (2009). Sustained activation of ERK1/2 by NGF induces microRNA-221 and 222 in PC12 cells. *FEBS Journal, 276*(12), 3269–3276.

Tremblay, R. G., Sikorska, M., Sandhu, J. K., Lanthier, P., Ribecco-Lutkiewicz, M., & Bani-Yaghoub, M. (2010). Differentiation of mouse Neuro 2A cells into dopamine neurons. *Journal of Neuroscience Methods, 186*(1), 60–67.

Visvanathan, J., Lee, S., Lee, B., Lee, J. W., & Lee, S.-K. (2007). The microRNA miR-124 antagonizes the anti-neural REST/SCP1 pathway during embryonic CNS development. *Genes & Development, 21*(7), 744–749.

Wang, Z.-M., Du, W.-J., Piazza, G. A., & Xi, Y. (2013). MicroRNAs are involved in the self-renewal and differentiation of cancer stem cells. *Acta Pharmacologica Sinica, 34*(11), 1374.

Wheeler, B. M., Heimberg, A. M., Moy, V. N., Sperling, E. A., Holstein, T. W., Heber, S., et al. (2009). The deep evolution of metazoan microRNAs. *Evolution & Development, 11*(1), 50–68.

Wienholds, E., Kloosterman, W. P., Miska, E., Alvarez-Saavedra, E., Berezikov, E., de Bruijn, E., et al. (2005). MicroRNA expression in zebrafish embryonic development. *Science, 309*(5732), 310–311.

Wienholds, E., Koudijs, M. J., van Eeden, F. J., Cuppen, E., & Plasterk, R. H. (2003). The microRNA-producing enzyme Dicer1 is essential for zebrafish development. *Nature Genetics, 35*(3), 217–218.

Wienholds, E., & Plasterk, R. H. (2005). MicroRNA function in animal development. *FEBS Letters, 579*(26), 5911–5922.

Xie, H.-R., Hu, L.-S., & Li, G.-Y. (2010). SH-SY5Y human neuroblastoma cell line: in vitro cell model of dopaminergic neurons in Parkinson's disease. *Chinese Medical Journal, 123*(8), 1086–1092.

Xue, Q., Yu, C., Wang, Y., Liu, L., Zhang, K., Fang, C., et al. (2016). miR-9 and miR-124 synergistically affect regulation of dendritic branching via the AKT/GSK3β pathway by targeting Rap2a. *Scientific Reports, 6,* 26781.

Yadav, S., Jauhari, A., Singh, N., Singh, T., Srivastav, A. K., Singh, P., et al. (2015). MicroRNAs are emerging as most potential molecular biomarkers. *Biochemistry & Analytical Biochemistry*. https://doi.org/10.4172/2161-1009.1000191.

Yadav, S., Pandey, A., Shukla, A., Talwelkar, S. S., Kumar, A., Pant, A. B., et al. (2011). miR-497 and miR-302b regulate ethanol-induced neuronal cell death through BCL2 protein and cyclin D2. *Journal of Biological Chemistry, 286*(43), 37347–37357.

Yang, S., Toledo, E. M., Rosmaninho, P., Peng, C., Uhlén, P., Castro, D. S., et al. (2018). A Zeb2-miR-200c loop controls midbrain dopaminergic neuron neurogenesis and migration. *Communications Biology, 1*(1), 75. https://doi.org/10.1038/s42003-018-0080-0.

Yao, C.-X., Wei, Q.-X., Zhang, Y.-Y., Wang, W.-P., Xue, L.-X., Yang, F., et al. (2013). miR-200b targets GATA-4 during cell growth and differentiation. *RNA Biology, 10*(4), 465–480.

Yu, J.-Y., Chung, K.-H., Deo, M., Thompson, R. C., & Turner, D. L. (2008). MicroRNA miR-124 regulates neurite outgrowth during neuronal differentiation. *Experimental Cell Research, 314*(14), 2618–2633.

Zhang, G.-Y., Wang, J., Jia, Y.-J., Han, R., Li, P., & Zhu, D.-N. (2015). MicroRNA-9 promotes the neuronal differentiation of rat bone marrow mesenchymal stem cells by activating autophagy. *Neural Regeneration Research, 10*(2), 314.

Zou, Y., Huang, Y., Yang, J., Wu, J., & Luo, C. (2017). miR-34a is downregulated in human osteosarcoma stem-like cells and promotes invasion, tumorigenic ability and self-renewal capacity. *Molecular Medicine Reports, 15*(4), 1631–1637.