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Review

Trans-Differentiation of Non-Stem Cells to Nerve cells or Neural Stem Cells through MicroRNA Reprogramming

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Abstract: Brain stem cells (neural stem cells or NSCs) and neurons of a chosen kind reprogramming is a potential technique for cell therapy. It is possible to reprogram non-neuronal cells, for example, by using a predetermined group of factors, nuclear transfer, and the induced transcriptional factors (TFs) expression in a related lineage of cells, and non-coding microRNAs (miRNAs). Researchers have additionally been attempting to improve reprogramming methods, whether it is by employing unique sets of biomolecules and particular TFs or by delivering relevant miRNA and Biomolecules. The technique of miRNA mediated is intriguing for its capability to quickly create a range of biologically desirable cell types for therapy from different lineages of cells. Current findings have made significant advancements towards changing the somatic cells to diverse particular neuronal subgroups with greater efficiency, using reprogramming of miRNA-mediated neural cells, despite the fact that the precise processes need to be discovered. To further understand how miRNAs might direct somatic cells to become neural, we need to look at the latest research on their function in neural reprogramming over the differentiated cells. Recent findings on the role of miRNAs in the initiation of cell reprogramming and the determination of the neuronal subtype's destiny are the primary focus of this comprehensive overview. Furthermore, we cover the far more latest results concerning certain miRNAs' activity in controlling different phases of neuronal differentiation, which contributes in comprehending the interaction network of miRNAs and their receptors.

Keywords: Neural stem cells, Reprogramming, Neurons, MicroRNA, Somatic cells, Trans-Differentiation, miRNA

1.Introduction

Cell metabolism, differentiation, proliferation and fate determination, are all affected by post-transcriptional gene regulation by microRNAs (miRNAs), which are tiny, endogenous short non-coding RNAs that range in length from 19 to 23 nucleotides [1–6]. By having a complementary sequence to an mRNA's 3′ untranslated region, miRNAs selectively identify and control the production of certain mRNAs. It is significant to note that a single miRNA may control a process by targeting many mRNAs, and that multiple miRNAs can each target a specific mRNA. Because miRNAs may either degrade or block translation of target mRNAs, they have the ability to affect the transcriptome, which can affect many biological

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processes [7, 8]. Numerous miRNAs, ranging from plants to mammals, have been discovered since the first miRNA was discovered in 1993 [9]. Additionally, it was shown that miRNAs have regulatory functions in several crucial cellular processes. When it comes to the either directly or indirectly cell reprogramming process, particular miRNAs were utilized to control the de novo DNA methylation that is in control of that reprogramming [10, 11]. Regenerative medicine has seen a surge in attention after Takahashi and Yamanaka revealed that only a few TFs may trigger the process of reprogramming forward into a pluripotency stage, Directing the reprogramming to a range of cell targets has also opened up various new research pathways since it prevents ethical problems and decreases immunological rejection [12, 13]. When it comes to cell reprogramming, multiple signaling pathways and transcription factors play critical roles in the complex gene expression regulation networks, this is particularly true in the most well-studied techniques [14,15]. Studies based on Yamanaka and colleagues' technique for converting fibroblasts to their desired cells have shown that multiple transcriptional regulators play an essential part in reprogramming and neurogenesis, and that certain Transcription factors including Nanog, Sox2, kif4 and Oct4 are sufficient to effectively produce neuro blasts, demonstrating that such Transcription factors exhibit substantial reprogramming potential [16–23]. Non-coding RNAs perform a significant function in the reprogramming process, however the exact control by these ncRNAs such as regulation of gene expression and epigenetic, is critical to the success of this process and the reprogrammed cell profiles' maintenance. Notably, certain miRNAs may cause mammalian somatic cells reprogramming, including fibroblasts, independently requiring enforced expression of many other Transcription factors. As a result, a sequential cell reprogramming process may benefit from the utilization of miRNAs to control the various steps of this process. In this article, we will go through the most current research on miRNAs' role as post-transcriptional controllers in regulating and coordinating cellular functions.

2.Reprogramming of Somatic Cells through a Novel Method

As gene silencers, miRNAs have historically been considered great regulator of gene expression. Transcription Factors-based compounds, instead of miRNAs, have been utilized in the majority of published studies on cell fate switches. However, recent studies have demonstrated that miRNAs could be utilized to reprogram cells and affect fates of neuronal cell. It has been found that a single TF may induce fibroblasts into neurons and NSCs, demonstrating a vital function for miRNA-9/9* and miRNA-124 during reprogramming of the cells and neural cell fates induction [24, 25]. In addition, there is an increasing amount of research that indicates various miRNAs, such as Let7 family, miRNA184, miRNA132, miRNA302/367 and miRNA137, perform a function in the reprogramming of the cell [52, 26–28]. In other words, the prevailing narrative that Transcription factors play a significant role in reprogramming of the cells has indeed been disproved. Despite extensive research on the crucial roles that certain components, miRNAs and signaling biomolecules play in reprogramming, the process behind miRNA-mediated cell reprogramming has not yet been fully uncovered. Methylation of DNA, which is an important factor in the development of mammalians, is widely recognized to establish the precise pattern of expression in the cells. Reprogramming Somatic cells requires the elimination of DNA methylation at the promoter of critical Transcription factors in stem cell [29]. To begin the reprogramming mechanism, the epigenetic modifiers which are involved in distinct forms of methylation of DNA will be targeted by certain miRNAs, this allows the apparatus of transcription to reach those genes and increase their expression more [29]. Since miRNA

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insufficiency generally causes demethylation of DNA, the reconfiguration of the pattern in methylation of DNA contributes in reprogramming of somatic cell because of the significance of demethylase in H3K4 and H3K9 for de novo methylation of DNA [52, 30–32]. By providing Transcription factors, this modification in methylation makes patterns of the gene expression resemble stem cells [52]. 3′-untranslated regions of mRNAs commonly include sequences of regulation processes, which promote RNA interference after transcription [33]. This kind of 3′untranslated regions may include both regulatory protein binding sites and miRNA [34]. This may be accomplished by binding to particular locations in the mRNAs' 3′ untranslated regions to prevent them from being translated or by inducing the destruction of those mRNAs themselves [35]. There may be silencer sequences in the 3′-untranslated regions that link to repressor proteins to reduce expression of mRNA and translation of protein [36, 37], an essential phase in reprogramming and maintenance of stem cells. NR2F2, a nuclear receptor that adversely controls Oct-4, is the target of miRNA-302, as it was recently documented [38]. The expression of Oct-4 rises when a site of methylation on the Oct-4 promoter is removed by global demethylation of DNA and simultaneously NR2F2 is reduced [54, 39, 40]. Reprogramming is made possible by the interaction of miRNAs with some other regulators and transcription factors. This connection is crucial in coordinating reprogramming and plays an important part in reprogramming processes of the cells. The functionality of Let7 has been found to be inhibited by an ESC-specific RNA binding protein named Lin28 [41, 42]. In other words, this reprogramming process might be regulated by factors other than miRNAs. As a result, the prominent function of miRNA in reprogramming is inadequate for somatic cells to acquire alternate morphological and biochemical phenotype characteristics since the process of reprogramming is dynamic and involves numerous epigenetic and transcriptional alterations [43]. Therefore, there should to be additional molecules involved in the reprogramming of biological processes. The factors Reprogramming like telomerase reverse transcriptase and large antigen of SV40 function in conjunction with particular Transcription factors to facilitate in the reprogramming process. Vitamin C, on the other hand, has been demonstrated to improve the efficacy in the reprogramming of somatic cells [44]. The processes behind miRNA-mediated reprogramming will therefore be better understood in future research aimed at discovering novel target genes and regulators of miRNAs.

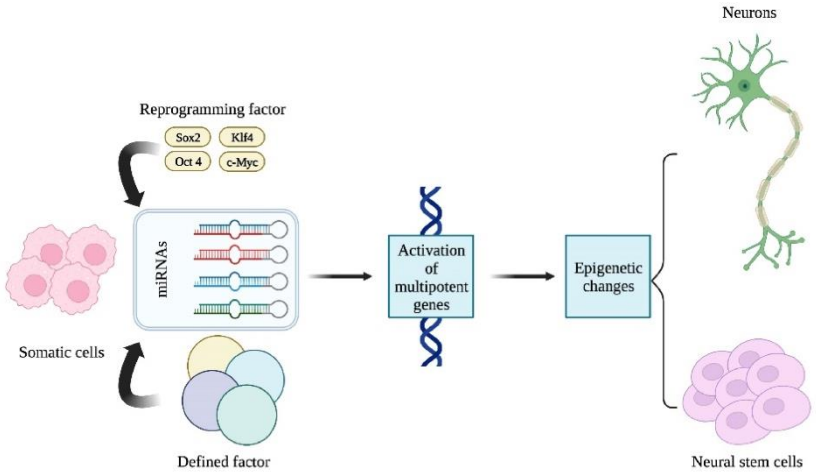

Figure 1. Trans-Differentiation of somatic cells to neural stem cells, as regulated by MiRNAs as well as other factors.

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3.Multiple Roles of miRNAs in Reprogramming

MiRNA-based cellular functions, such as reprogramming, cell differentiation and proliferation and a long with the stemness maintaining, have indeed been extensively examined to assess the therapeutic implications of this method. This is because strong evidence suggests that non-stem cells may be converted into Induced pluripotent stem cells (iPSCs) by epigenetic reprogramming through enforced over-expression of the specified transcription factors. In spite of advances in DNA-based reprogramming, however it continues to be the significant problem for potential arbitrary installation of reprogramming agents into the genome, that would end in disruption of genome. The utilization of numerous small compounds and particular miRNAs, as well as various combinations of Transcription factors, to promote pluripotency or reprogram iPSCs has indeed been studied in an attempt to enhance both the effectiveness as well as the safety of these techniques. MicroRNA study revealed that, in comparison of developed cells and stem cells from various sources had a unique miRNA expression pattern [45]. It is because of this that scientists are now reprogramming cells utilizing miRNAs. Interestingly, a necessary requirement is the involvement of certain particular Transcription factors regardless of the patterns types employed for reprogramming differentiated somatic cells. NSCs (neuronal stem cells) may be generated from fibroblasts by combining Transcription factors such as c-Myc, Nanog, Sox2, kif4 and Oct4 according to new findings [12, 15, 46, 47]. Differentiated Somatic cells may be induced to become separate lineage cells by certain compounds and growth factors [48–50]. It has also been shown that miRNAs engage numerous biomolecules, such as transcription factors (TFs) and many other regulation factors that are directly participating in Trans-differentiation or reprogramming of the cell, indicating that this boosts the effectiveness of TF-mediated reprogramming outlined [51–57]. The capability of miRNAs to convert initial differentiation somatic cells into pluripotent stem cells has lately been shown in multiple research. That is also likely due to miRNAs' role in the regulation of variables associated with pluripotency stage. As an instance, miRNA302 controls the pluripotent markers expression such as Nanog, Sox2, SSEA3/4 and Oct-4 [58, 59], leading to dmnt downregulation and demethylation of DNA [58]. Ultimately, these actions lead to reprogramming of differentiated somatic cells. In case that wasn't particularly impressive enough, certain tiny biomolecules like CHIR 99021, BIX-01291 and SB431542 were shown to operate as Transcription Factors [49, 50 ,60,61]. Analysis of the reprogramming processes has demonstrated that regulation of miRNA is closely connected to a variety of molecules [61]. Although miRNAs may regulate an enormous and complicated gene expression network [62] across many different developmental and cell functions, they are particularly well suited to this task. The sequence-specific identification of target sequences and Assemblies of effector proteins termed Bmicro-ribonucleoprotein (BmiRNP) are being used to control gene expression [62]. When the interaction of miRNA-mRNA occurs, it has the power to suppress the beginning of transcription or translation [63]. As a result, miRNAs, which directly or indirectly target the genes that participate in cell reprogramming and regulate their expression, will prevent it from happening. There are several examples of how miRNA-34 leads to iPSC synthesis through reprograming, for example, by targeting P53 [64]. Additionally, it has been claimed that members of the let-7 group prevent reprogramming [65, 66]. Many miRNAs, despite common thought, may promote the translation and expression of genes in particular types of cells and circumstances. The upregulating of genes by miRNAs may contribute in reprogramming of the cells [67]. It is

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possible that boosting or blocking expression of specific mRNAs via miRNA-mediated gene regulation will have unique effects on reprogramming of the cells [68]. As a result, miRNAs may either accelerate or prevent the production of triggered stem cells Even though Transcription Factors transmission through viruses, activation growth factors or small biomolecules, and transport of chemical compounds may all contribute in reprogramming of the cell, the miRNA-mediated method was demonstrated to be significantly effective compared to the more regular techniques [54]. Beyond the lack of genome integrating issues, miRNA function by itself controls reprogramming and the efficiency of this performance.

4.Major MiRNAs in Somatic Cell Neural Reprogramming

4.1. MiRNA-9

In the brain, miR-9 is likewise abundant [90] and has been preserved throughout evolution [69]. Neuronal migration, subtype determination, differentiation and proliferation are all significantly influenced by miR-9 [5, 70, 71].In addition, miRNA-9 maintains the dynamic equilibrium of migration and proliferation of NPs throughout formation of CNS [5]. According to recent research, miRNA-9 has a variety of functions in the brain axis of various species and regions [72]. Stathmin (Stmn1) is the target of MiRNA-9, which prevents migration of neural precursor and promotes a more developed NP fate [5]. There are numerous other targets of miRNA, like Gsh2, which performs an initial function in the formation or migration of the ventral telencephalon (medialgan glionic eminence or MGE and lateral ganglionic eminence or LGE) and controls fate of stem cells, as well as Tlx, which acts as a key player in stem cell differentiation[73]. Increased stem cell differentiation rates in stem cell are associated with the suppression of the TLX transcription factor (74,75). It has also been demonstrated miRNA-9 regulates the proliferation of NPCs through Cyclin D1 mRNA targeting [76]. In the zebrafish, her9 and her5, two anti-neurogenic genes, as well as the FGF signaling genes, are targeted via miRNA-9, triggering the formation of the midbrain-to-hind brain borderline [77]. It has also been proposed that Hairy1 is a target of miRNA-9 involved in promoting proliferation of the cell [72]. According to Gsh2, a nuclear cytosolic transcription factor named Fork Head Box G1 (Foxg1) is necessary for layering and patterning of the cerebral cortex, cell migration and telencephalon development in vertebrates [78, 79]. Neurogenesis is regulated by Foxg1 throughout the initial stages of cortical development via maintaining progenitor cells in a proliferating mode and limiting their differentiation to neurons [80]. For the first time, it has been found that miRNA-9 is involved in regulating the formation of pre-motor neurons of ganglionic autonomic and spinal cord via Foxg1 targeting [80]. It is remarkable that REST and miRNA-9 have a reciprocal effect on each other. Through interacting with a conserved repressor element (RE1) in the loci of neuronal gene and attracting the co-activator multiplex made up of the methyl CpG binding protein MeCP2 and histone deacetylases, REST inhibits neuronal genes expression in non-neuronal cells [81, 82]. In progenitors, increasing in expression of miRNA-9 facilitates the shift to neurons in the post-mitotic stage. As a result, r educed REST activity in cells leads to an increase in the expression of neuronal genes. BAF53a expression in human fibroblasts may be suppressed by miRNA-9/9*-124 in parallel to REST and co-REST [82, 83].

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As with suppressing the REST, Co-REST and PTBP1 expression, inhibiting BAF53a also causes fibroblasts differentiation to neurons [82, 84]. There is evidence to indicate that the BAF53a and BAF45a targeting by miRNA-9/9* is necessary for post-mitotic activities, according to our study [82]. In this way, miRNA9/9* has been proven to function on several targets in a programmatic manner. Therefore, the activities of miRNA-9 unique target genes are indeed influenced by the timing of CNS formation, various differentiation programs of neural cell, and even across different animal species.

4.2. MiRNA-25

Evolutionary preserved miR-106b25 cluster contains the miRNA-25 gene. Three distinct mature miRNA types, miRNA-25, miRNA-106b and miRNA-93, are encoded by this cluster, which is situated in the Mcm7 intronic sequence [85, 86]. Cell proliferation and apoptosis are two of the functions of the miR-106b~25 cluster. Proliferation of NSC in adults seems to be dependent on the miRNA-106b~25 cluster, according to recently published findings [87, 88].

p57, a cell cycle inhibitor, is directly regulated by miRNA-25, which has been confirmed as a target of miRNA-25. To put it simply, Cdk inhibitors, such as p57, which is a member of Cip/Kip family, halt progression of the cell cycle through all the phases of G1 and S, therefore it operates as a cell cycle brake [89]. It has also been established that miRNA-25 is crucial for pluripotency maintenance and reprogramming, as well as self-renewal stem cell and differentiation [88, 89]. It was also discovered that miRNA-25 controls an E3 ubiquitin ligase termed Wwp2, which, specifically targets Oct4, as well as Fbxw7, a regulator of Klf5 and c-Myc [90]. To support this, potential prospective targets for miRNA-25, including nitric oxide signaling, TGFβ, insulin/IGF and p53, were considered crucial controllers of stemness preservation and neural differentiation [88]. However, further research is necessary to confirm the molecular functions of these targets and how they interact with one another during the reprogramming of the cells.

4.3. MiRNA-124

All kinds of organisms have the same miRNA-124. It is one of the most well-known and common miRNAs in the CNS, representing between 25–48% of total brain miRNA [91–93]. Neurons express MiRNA-124, whereas other CNS cells like NSCs and glial cells do not. Microglial cells also produce MiRNA-124, and this expression is decreased in active microglia [94–96]. The expression of miRNA-124 in NSCs only starts when NSCs become neuro progenitor (NP) cells [97]. This miRNA-124 enhances neuroblast cell cycle exit and is expressed at its maximum level through the processes of neuronal differentiation like neurite outgrowth in the SVZ or sub ventricular zone of the brain, according to multiple findings. Glioblastoma cells are inhibited in cell differentiation and cell proliferation when miRNA-124 is delivered via lentiviral vectors [25, 97–99]. In both cultivated embryonic cortical NPs and NSCs, overexpression of miRNA-124 inevitably led to a neuronal phenotype [100]. MiRNA-124 expression was inhibited in vitro by providing antisence2′-Omethyl AMO, which restricted commitment of neuronal fate while promoting NSC proliferation [98]. MiRNA-124 seems to serve a key function in controlling neurogenesis throughout the formation of neuron, based on these researches. When it comes to neurogenesis of

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the spinal cord, Cao et al, discovered that miRNA-124 was less relevant than previously thought [101]. As a result, the function of miRNA-124 in the human body is still unknown and questioned. Many targets for miRNA-124 have been discovered and validated in virtue of the significance of miRNA in neurogenesis. As a neuronal phenotype controller, miRNA124 has been identified as the primary target of REI silencing transcription factor (REST) [102, 103]. Neuronal gene expression is facilitated through the inhibition of REST by miRNA-124. However, REST by repressing miRNA-124 also blocks the neural genes expression in non-neural cells[104]. In non-neural cells, a protein termed poly pyrimidine tract-binding protein 1 or Ptbp1, functions as an inhibitor of alternative splicing. This protein seems to be another target of the miRNA-124. The neuronal pro transcriptome is increased by MiRNA-124, which targets Ptbp1 and suppresses non-neuronal genes substantially [105]. If you want to transform your fibroblasts into neurons you have to increase the expression of miRNA-302/367 cluster which is the pluripotency stem cell-specific miRNA, as well as two additional miRNAs that are neuron-specific, named miRNA-9/9* and miRNA-124 [28]. MiRNA-124 regulates Ptbp1-mediated alternative splicing in this study, allowing fibroblasts to undergo reprogramming and eventually acquire a neural fate. Jagged1, a ligand for Sox9 and Notch, is among the other targets. The ability of NSCs to self-renew and to suppress differentiation is dependent on Jagged1 [96, 106, 107]. MiRNA-124a dramatically decreased Jagged1 expression and level of proteins in neuro-progenitor cells, leading to Notch signal inactivation, which eventually leads to neuronal differentiation and cell cycle exit [156]. Jagged1 regulation was shown to be mediated by miRNA-124a according to the studies. A HMG-box transcription factor termd Sox9 is a key player in various differentiation pathways, including chondrogenesis, sex determination, gliogenesis, formation of the heart, neural crest differentiation, hair follicle function and prostate, retina, pancreas development [108–110]. In addition, Sox9 plays an important role in regulating cell proliferation. When neuroblasts and fibroblasts, two somatic cells, produce high levels of miRNA-124, cell growth may be dramatically reduced, but inhibiting miRNA-124 can increase cell proliferation, confirming that miRNA-124 may significantly influence Sox9 expression. Furthermore, the suppression of Sox9 via miRNA-124 plays a critical function in the SVZ stem cell lineage's development to neurons. Sox9 regulates neuronal development in this way in addition to regulating proliferation of the cells [96]. Additionally, miRNA-124 target genes may initiate a neuronal program along with miRNA-124 and certain other biomolecules, indicating that miRNA-124 performs essential function in setting up and creating a neural transcription network in reprogramming of somatic cells (Table 1). A molecular technology approach to reprogramming of the cells into brain cells may be established under the perspective of these functional data on miRNA-124 and its targets.

4.4. MiRNA-302/367

In early embryogenesis, miRNA-302/367 is relatively abundant and quickly drops after differentiation [111], and multiple investigations have revealed that the miRNA-302/367 functions as an upstream pluripotency controller to influence the expression of Nanog, Oct4, Sox2, and other embryonic transcription factors [29, 112, 113]. A global demethylation is induced as a result of the many epigenetic mechanisms targeted by MiRNA-302/3667. For certain transcription factors that are only found in premature zygotes, global DNA demethylation proceeds at binding site of the promoter during the 1–8 cell stage or blastocyst

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phase. The co-activation of genes of pluripotent is caused by the silencing of histone demethylases 1 and 2 (AOF1 and AOF2) that are lysine-specific and methyl CpG-binding proteins 1 and 2 (MECP1-p66 and MECP2) by MiRNA-302 [57, 33]. NR2F2, a transcription factor from the family of nuclear orphan receptor and a negative controller of Oct4 is another target of miR-302/367 [38]. Many investigations have also demonstrated that Sox2, Nanog and Oct4 attach to the miR-302/367 promoter, increasing the expression of this microRNA [39]. To promote the expression of Oct4 and raise the level miR-302/367, miRNA-302/367 causes global demethylation and decreases the expression of NR2F2. Other transcription factors, namely as Nanog and Sox2, are triggered as a result of this reciprocating cycle, that elevates the levels of Oct4 and miRNA302, 367 [54, 114]. Co-expression of Nanog, Sox2 and Oct4 and Global demethylation may be caused by miRNA-302/367 overexpression, which in turn can contribute to iPSCs in human (Table 1). The reprogramming of fibroblasts becoming neurons was repeatedly triggered by the miRNA-302/367 overexpression, which is exclusive for pluripotency stem cells, in conjunction with the miRNAs such as miRNA124 and miRNA-9/9*, which are also exclusive for neurons [115]. MiRNA-302/367 was reported to convert astrocytes becoming neuroblasts as well as in vitro and in vivo in human adults, by Ghasemi-Kasman. Reprogramming through miRNA-302/367 targets Oct4, which is an epigenetic factor to transform astrocytes into neuroblasts in the treatment of valproic acid (VPA) [116]. iPSC production efficacy is correlated with miRNA-302b and 372 sites, which include the RHOC or ras homolog family member C and TGFBR2 or transforming growth factor beta receptor II [117]. The transition G1 to S is inhibited by miRNA-302/367, which also targets cyclin E-CDK and cyclin D-CDK4/6 [118].

With regard to self-renewal of stem cell and various capabilities of differentiation, miRNA-302/367 exerts a critical function in reprogramming of somatic cells, as well as an important part in pluripotent stem cells (Table 1). MiRNA-302/367 also induce mesenchymal epithelial transition (MET) by limiting translation of the gene, preventing cell cycle progression, controlling epigenetic alteration and the expression of differentiation-associated gene and functioning effectively in reprogramming of somatic cells due to its conserved area [119].

4.5. MiRNA-137

A short non-coding RNA termed miRNA-137 controls other genes expression through the use of range of methods. Several kinds of cancer have been linked to the miR-137, which is a tumor suppressor on the human chromosome 1p22. There was evidence that miRNA-137 was expressed throughout the nervous system, not only the adult NSCs, but the hypothalamus, cerebral cortex, amygdala, and hippocampus [120, 121]. MiRNA-137 has lately been shown to control the differentiation of embryonic stem cells in mouse and proliferation of NSC, as well as neuronal maturation, including the spine density in neuronal development of hippocampus and stimulation of dendritic morphogenesis and [96, 122]. In the formation of mouse embryonic stem cells, cell cycle signaling, and a number of human malignancies, multiple targets of miRNA-137 have been identified and discovered to play important functions (Table 1)[123, 124]. A total of 32 genes were discovered as miRNA-137 targets Balaguer et al. [125, 126]. It has been demonstrated that miRNA-137 binds to the 3′-UTR of lysine-specific histone demethylase 1A or LSD1, which is one of Balaguer's targets. LSD1 has been observed to inhibit TLX transcription, suggesting that miRNA-137 is essential for undifferentiated phenotype preservation [122, 127].

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Additionally, numerous investigations have discovered the Rho Cdc42 (cell division cycle 42) a member of GTPase family, as a primary target for miRNA137. Cdc42 is linked to the activation of cell cycle arrest in G1 that leads in NSCs differentiating into neurons and colorectal and glioblastoma tumor cells developing and/or proliferating less rapidly [122]. As a result, miRNA-137 inhibits the signaling Cdc42/PAK and thereby decreases the progression of G0/G1 cell cycle, cancer cell invasion, and proliferation and [128]. It has also been demonstrated that in adulthood, miR-137NA actively suppresses the expression of CDK6 and reduces the quantity of CDK6 downstream target, the phosphorylated RB. This is considered the process through which NSCs of adult mouse, SCs produced from oligodendroma, and SCs derived from human glioblastoma multiform induce differentiation and decrease proliferation [96]. Additionally, Mind Bomb-1 or Mib1 is a recognized ubiquitin ligase that plays an important function in neurodevelopment and neurogenesis and is also the target of miRNA-137 [129]. Another primary target for miR-137 in ESCs has just been identified as Jarid1b formerly recognized as KDM5b, which is a demethylase for histone H3 Lysine 4. The ESC undifferentiation phenotype is maintained by the regular expression of Jarid1b throughout the embryogenesis of mouse. MiR-137 is thought to have a function in preventing the ESCs differentiation by reducing Jarid1b [130]. In order to preserve the proper proliferation of NSCs but without reducing their capacity to differentiate the expression of miRNA-137 must be tightly controlled.

A control loop was established between LSD1 and miRNA-137 to keep the equilibrium between NSC differentiation and proliferation. Therefore, throughout the formation of CNS, the control loop regulates the balance between differentiation and proliferation.

4.6. MiRNA-200

It is believed that two distinct miR-200 clusters exist in the human genome, each containing a subset of these genes. These two clusters may be found in the areas of the genomes of miR-200a and miR-200b alternatively. On the one hand, there are clusters including the microRNAs 200a, 200b and 429; on the other, there are clusters containing the microRNAs 200c and 141 [131, 132]. Several proteins in the tumor microenvironment are specifically targeted by the miR-200 family members, which are abundant in epithelial tissues and play a crucial role in tumor formation, progression, and intravasation. The Zeb1 or zinc finger e-box bind homeobox 1 and Zeb2, the transcriptional repressors of E-cadherin target MiRNA-200, enhancing cell motion and causing EMT [131, 133, 134]. In the nervous system, E2F3 and Sox2 mRNAs are specifically targeted by the miR-200 via unique binding sequences (BSs) in their 3′-Untranslated regions, which has been demonstrated to enhance the neural progenitors of ventral midbrain/hindbrain (vMH) in differentiation of neurons and the cell cycle exit [135]. Neural stem cells or progenitor cells need Sox2 to preserve their ability to differentiate into glial cells or neurons, however the amount of Sox2 needed is dose-dependent (Table 1) [136–138]. MiR-200, a miRNA subtype abundantly and exclusively produced in the embryonic olfactory system, was also discovered by Choi et al, to have significant roles in regulating differentiation and determining the progenitor fate in the olfactory system [139]. The loss of miR-200 activity affects the final olfactory progenitor cells differentiation, as shown by the mature olfactory marker reduction of expression and the increase of foxg1, the immature olfactory primordium marker [139]. MiR200 family

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expression is also linked to differentiation of neurons by suppressing the expression of Klf4 and Sox2, and to the conversion of neural epithelial cells into Neural Stem Cells [140,141]. Furthermore, the family of miR-200, through targeting particular Zebs, influences the options of ESC differentiation regarding whether to differentiate into meso-endodermal cells or ectodermal cells at a young stage. Such studies reveal the intricacies of the miRNA regulation network in modifying neuronal differentiation.

4.7. MiRNA-134

In the mammalian group of miRNA379-410, miRNA-134 is a member of microRNA precursors' family that is exclusively transcribed in the brain of mammals [90, 140]. It is located particularly in neurons of hippocampus in rats and may serve to passively control the formation of synapses [141, 142]. It is expressed only in the neurons of hippocampus in rats and has the potential to influence synaptic formation in an indirect manner [143, 144]. Ischemia/reperfusion has been demonstrated to greatly increase the production of miRNA-134, which might result in the death of neurons [145]. The functions and targets of this miRNA vary based on the stage of brain development. Dcx and Chrdl-1 are controlled by miRNA-134, which increases the proliferation of cultured cortical neural precursor cells and inhibits apoptosis process [146]. MiR134 has been demonstrated to target the HSPA12B protein, and reducing its expression in the brain might provide neuroprotective effects against ischemia damage both in vivo and in vitro [147]. There has also been evidence that miRNA379-410 cluster members such as microRNA 543, miR-496, and microRNA 369-3p control proliferation in the central nervous system development [140]. Premature migration of neurons may be induced by these miRNAs that interfere with the regulation of N cadherin [148]. To regulate proliferation of the cells and carry out other cell type-specific roles in the biological system, this triple of miRNA precisely regulates the levels of their target molecules. Table 1 provides a summary of the targets and functions of miRNA-134.

4.8. Let-7

As the first miRNA identified in C.elegans, Let-7 is also detected in humans and other organisms [147]. Let-7 is the family of miRNA with the greatest expression in NSCs/NPs, according to research [94]. MiRNA generating from Let7a to Let7i has a variety of mature isoforms. [148]. When it comes to fate-determining functions, differentiation and neurogenesis in the Central nervous system, Let-7 has been shown to perform a variety of roles (Table 1). In embryonic stem cells or ESCs, Let7a targets lin-28 that suppresses pre-let-7 activation via Dicer [149]. Many of the cell cycle-related genes are regulated by Let7b, including TLX and CycleD1 [149]. Decreased proliferation and increased neuronal differentiation are the outcomes of NSC overexpression of Let-7b [149]. Let-7d Let-7c have comparable functions in the regulation of self-renewal genes in somatic cells.

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Neuronal migration, differentiation and NSC proliferation of NSC are suppressed when TLX is down regulated [160, 150]. Let-7d may be used to facilitate the bioprocess. In spite of the discovery of multiple let-7 targets, extensive research is necessary to comprehend the let-7 signaling networks that control reprogramming of the cells. Following such studies, it is indeed conceivable that somatic cells may be driven into neuronal or NSC dedication utilizing miRNA sponge technology [149].

Table 1. What we know so far about the molecular functions and targets of the miRNAs described in the article.

miRNA	Species/ targets	Molecular functions	Reference
miRNA-9	zebrafish: Her5/Her9, Fgf8-1, FgfR1 mouse: Stmn, Map1b, Rest, Hes1, Gsh2, TLX	**establishment** of the midbrain/hindBRAIN **borderline**, **Reduction** in neural progenitor **cell division**; **promotion** of neuronal fate and **motor** neuron differentiation; **increase** in microtubule production	[5, 25, 53, 71–73, 76, 77, 81]
miRNA-9*	mouse: BAF53a, BAF45a, Co-Rest	**activation** of the neurogenic fate	[25]
miRNA-25	mouse: Fbxw7 zebrafish: p57	**Reactivation** of the **cell cycle** and **promotion** of **proliferation** of the cells	[23, 66]
miRNA-124	Aplysia: CREB mouse: Lhx2, EphrinB1, Ptbp1, SCP1, BAF53a, Sox9, Jagged1,	**inhibition** of alternative splicing of neuronal genes in **non-neuronal tissues**, **activation** of the neurogenic fate, **stimulation** of axon genesis cell **cycle exit** and neuronal **differentiation and Enhancement** of the neural **transcriptome**	[25, 82, 95, 97, 104, 105, 162]
miRNA-302/367	mouse: Cyclin D-CDK, Cyclin E-CDK human: Oct4, NR2F2, AOF1, AOF2	**Inducing** global demythylation to **maintain cell self-renewal** and **various** differentiation **abilities**	[33, 38, 57, 115, 117]
miRNA-137	mouse: Mib1, Jand1b, Cdk6, Ezh2, LSD1, Cdc42	**halting** the **G1 phase** of the cell cycle, **Promotion** of neuronal differentiation and **inhibition** of neural stem cell proliferation	[96, 120, 121, 128]
miRNA-200	mouse: E2F3, Sox2, ZEB2, ZEB1	**Increase** of ventral midbrain/hindbrain neural progenitors and **facilitation** of cell **cycle exit**	[129, 131, 137]
miRNA-134	rat: Limk1 mouse: Chrdl-1, Nanog, Sox2, DCX	**Inhibition** of neurogenesis, enhancement of **cell survival**, **suppression of apoptosis**, **promotion of ectodermal** differentiation and **Reduced self-renewal** capacity	[144, 165, 166]
Let-7	mouse: TLX	**Enhancement** of the **differentiation** of neurons	[163]
Let-7a	mouse: Lin28, Pax6	Neuronal **lineage dedication** and **regulation** of **dopaminergic** differentiation	[149, 164]
Let-7b	mouse: Lin28, Hmga2, CyclinD1, TLX	**Promotion** of neuronal differentiation, **inhibition** of neural progenitor **growth**, and **facilitation** of cell **cycle exit**	[149, 163]
Let-7d	mouse: TLX	the **establishment** of neural differentiation and migration, cell **growth inhibition**	[137]

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5.MiRNA Synthesis

In C. elegans, miRNAs were first identified during a genetic test to discover molecules controlling development of nematode [9, 151]. Since the most of the identified miRNA genes are intergenic or antisense to nearby genes, it is likely that they are transcribed as separate parts which all include one or even more hairpin structures, which are made up of a terminal loop and a stem [1]. The sequential process of producing miRNAs from lengthy double-stranded RNAs may either be non-canonical (Drosha/Dgcr8-independent) or canonical (Drosha/Dgcr8 reliant) [152]. Animals go through the following steps to make canonical miRNAs:

(1) Transcription of miRNA loci and more modification to synthesized segments called, pri-miRNA using RNA polymerase II and certain associated protein.

(2) Utilization of type III RNase Drosha complex in the nucleus to convert pri-miRNA into precursor miRNA or pre-miRNA [153].

(3) The delivery of pre-miRNA with nucleo-cytoplasmic transport factor Exportin5 to the cell cytoplasm [154].

(4) Utilization of the second type III RNase endonuclease termed Dicer to produce 21 or 22 double shape containing miRNA* and miRNA [2].

Following this process, the RNA-induced silencing complex (RISC) selectively integrates one guide strand of the miRNA duplex, which serves to regulate the miRNA response elements (MREs) binding to particular mRNA transcripts by incomplete base pairing [155, 156]. Fig. 2 depicts a schematic layout of the potential pathways for miRNA synthesis, which aids in comprehending the procedure. Because of this, it is often considered that miRNA*, or the "passenger strand," is just a carrier strand that is eventually destroyed and rendered ineffective by numerous exoribonucleases [157, 158].

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Pre-miRNAs may also be produced through a non-canonical mirtron route [159, 160]. When host genes are transcribed, small introns containing potential hairpins enter the mirtron pathway, resulting in the generation of mirtrons. RanGTP and Exportin5 actively transport this pre-miRNA from the nucleus to the cytoplasm when lariat debranching enzyme (Ldbr) produces shorter pre-miRNAs that abut intron-exon boundaries [161]. Dicer cleaves pre-miRNAs to 22 nucleotides at the cleavage site of Drosha, resulting in an incomplete duplex comprising the mature version of miRNA and the complementary sequence of it taken from the opposite arm of pre-miRNA [1]. Genes' protein-coding regions include transcripts from which intragenic miRNAs are produced (Fig. 2).

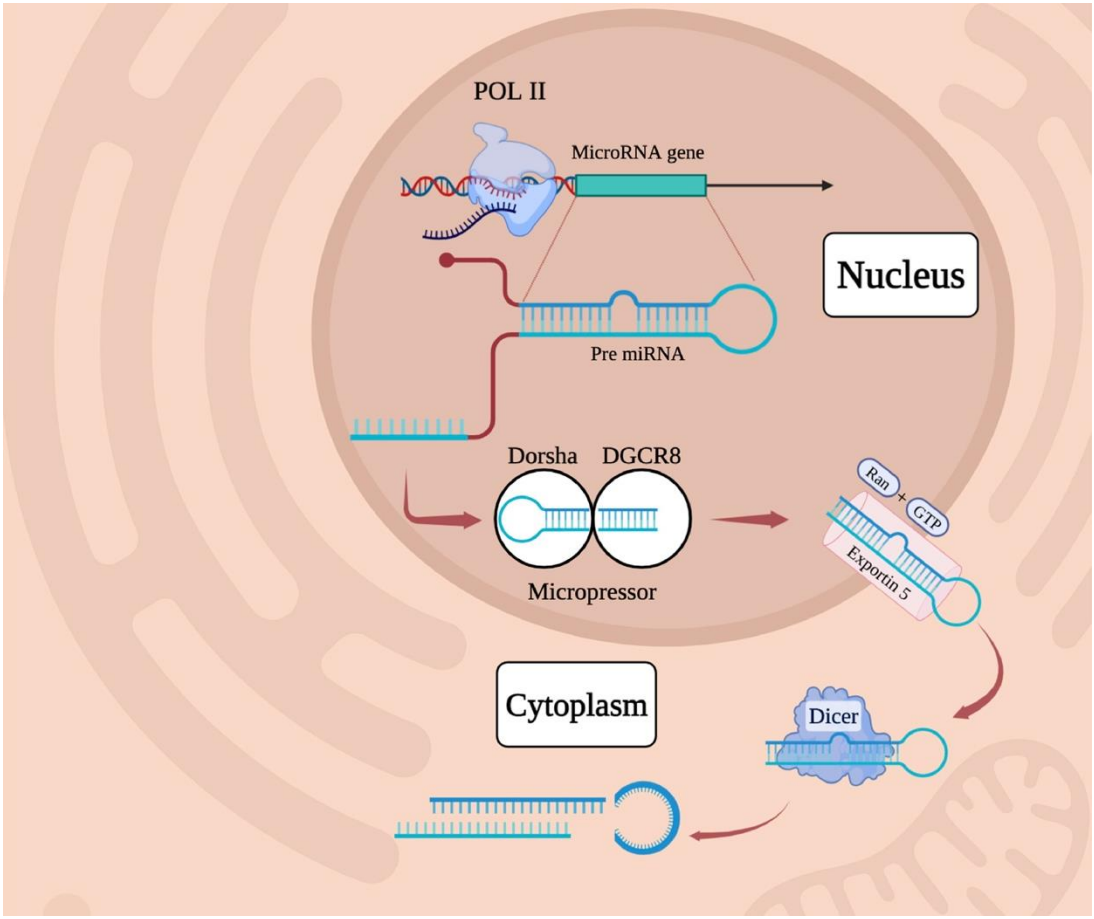

Figure 2. A schematic depiction of MiRNA Synthesis

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7.Conclusion

The reprogramming of Somatic cells is a complex process that requires a deep understanding of the functionality and control of miRNAs. MiRNAs, particularly neural cell-specific miRNAs, may trigger reprogramming processes comparable to those of small biomolecules such as Yamanaka factors, based on the effective production of NSCs utilizing a miRNA-mediated approach. There are several advantages of using miRNAs over traditional reprogramming methods, including the ability to effectively and directly modify the proteome and transcriptome in human adults. Furthermore, NSC-targeted miRNAs have been demonstrated to modify cell proliferation and biological phenotype, resulting in cell reprogramming, in addition to that, the NSC-targeted miRNAs affects cell cycle progression. The reprogramming based on miRNA might be effective for improving existing reprogramming procedures and might even give innovative techniques for future neural cell and NSCs production to cure neurodegenerative conditions and Central Nervous System damage. However, the biological process whereby NSC-specific miRNAs divert somatic cells to achieve pluripotency has to be actively investigated. For this reason, the study of miRNAs to control expression of the gene in specific locations and at certain times is a vital ingredient of neuro regenerative medicine's quest to better understand how these circuits are regulated throughout and reprogramming processes. MiRNA-mediated cell phenotypic alteration through targeted inhibition should, however, depend upon cooperation with other biomolecules, like reprogramming and transcription factors, since the mechanism of reprogramming itself is so complicated. The reprogramming is coordinated by a feedback mechanism between transcription factors, target biomolecules and miRNAs. Numerous approaches exist for somatic cells reprogramming to Neuronal stem cells effectively, particularly converting to neurons (Fig. 1). Although the control systems of miRNAs and their therapeutic implications remain largely unexplored. MiRNA-mediated reprogramming might be used to make brain cells and drug evaluation for cell therapy in diseases like neurodegenerative conditions and spinal cord injury.

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