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REVIEW

MicroRNAs as novel regulators of stem cell fate

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Abstract

Mounting evidence in stem cell biology has shown that microRNAs (miRNAs) play a crucial role in cell fate specification, including stem cell self-renewal, lineage-specific differentiation, and somatic cell reprogramming. These functions are tightly regulated by specific gene expression patterns that involve miRNAs and transcription factors. To maintain stem cell pluripotency, specific miRNAs suppress transcription factors that promote differentiation, whereas to initiate differentiation, lineage-specific miRNAs are upregulated *via* the inhibition of transcription factors that promote self-renewal. Small molecules can be used in a similar manner as natural miRNAs, and a number of natural and synthetic small molecules have been isolated and developed to regulate stem cell fate. Using miRNAs as novel regulators of stem cell fate will provide insight into stem cell biology and aid in understanding the molecular mechanisms and crosstalk between miRNAs and stem cells. Ultimately, advances in the regulation of stem cell fate will contribute to the development of effective medical therapies for tissue repair and regeneration. This review summarizes the current insights into stem cell fate determination by miRNAs with a focus on stem cell self-renewal, differentiation, and reprogramming. Small molecules that control stem cell fate are also highlighted.

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Key words: MicroRNA; Stem cell fate; Differentiation; Self-renewal; Reprogramming; Small molecule

Core tip: Stem cells are important in regenerative medicine applications due to their capacity to self-renew and differentiate into specific cell types. MicroRNAs (miRNAs) are short non-coding RNAs that negatively regulate gene expression at the post-transcriptional level. Recent studies suggest that miRNAs are key molecules in the regulation of stem cell fate decisions; this regulation is manifested as the fine tuning of cell- and tissue-specific gene expression. This review summarizes the current insights into stem cell fate determination by miRNAs and focuses on stem cell self-renewal, differentiation, and reprogramming. Small molecules that control stem cell fate are also highlighted.

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INTRODUCTION

Stem cells are a potential source for regenerative medicine and tissue engineering applications. These cells have the dual capacity to self-renew and differentiate into multiple distinct cell lineages[1,2]. These cells are classified as embryonic stem cells (ESCs), non-embryonic adult stem cells, and induced pluripotent stem cells (iPSCs). ESCs are pluripotent cells produced within the inner cell mass

of a blastocyst stage embryo 4-5 d post-fertilization and can differentiate into all three germ layers: ectoderm, endoderm, and mesoderm[3]. In contrast, adult stem cells are found in various tissues and organs, including the brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, and skin[4]. Some adult stem cells are multipotent; they can produce a limited number of differentiated cell types from their specific tissue of origin. iPSCs are reprogrammed to be embryonic-like stem cells from adult somatic cells[5,6].

Stem cell fate is controlled by transcription factors, epigenetic regulation, and non-coding RNAs[7,8]. Transcription factors are well-known for regulating gene expression, by either directly or indirectly binding DNA elements, and for their role in epigenetic regulation, such as DNA methylation and histone modification. The control of gene expression also occurs during the post-transcription process. Recent findings have shown that small non-coding RNAs are involved in cell fate decisions, including the maintenance and differentiation of stem cells[7,9].

MicroRNAs (miRNAs) are single-stranded, small non-coding RNA molecules. miRNAs modulate gene expression by either inhibiting mRNA translation or inducing mRNA degradation, which results from the complete or incomplete binding to the 3' untranslated region (3'-UTR) of specific mRNAs[10,11]. More than 1000 different mature miRNAs have been discovered in humans, and they regulate one third of all protein-coding genes[12,13]. Computational predictions of miRNA targets, functions, and expression, are accessible on multiple online prediction databases, such as TargetScan (http://targetscan.org), microRNA.org (http://www.microrna.org), miRBase (http://www.mirbase.org), PicTar (http://www.pictar.org), and miRWalk (http://mirwalk.uni-hd.de)[14,15]. One miRNA can target a large number of mRNAs, and/or many miRNAs can bind to one specific mRNA. This versatility may result in miRNAs mediating the effects of biological processes such as stem cell fate switches, proliferation, maintenance, and apoptosis. Interestingly, the first two miRNAs discovered, *lin-4* and *let-7*, were characterized during the developmental stage transition in *C. elegans*[16,17]. By deleting enzymes involved in miRNA processing and maturation, namely, Dicer or Dgcr8, studies have shown that miRNAs are important in maintaining ESC pluripotency and differentiation capacity[18-20]. miRNAs also play a role in the differentiation and self-renewal of mesenchymal stem cells (MSCs)[21]. Many observations suggest that miRNAs critically regulate stem cell fate decisions, including self-renewal, differentiation into specific lineages, and reprogramming. Thus, this review focuses on miRNAs that are powerful regulators of stem cell fate. Furthermore, we discuss the potential of small molecules in regulating stem cell fate.

MICRORNAS IN MAINTENANCE

Self-renewal and differentiation potential are hallmarks of stem cells. Self-renewal is a process of symmetric division into two daughter cells. To self-renew, stem cells must proliferate without differentiating or becoming apoptotic to maintain their undifferentiated state[22,23].

Cell division during self-renewal is achieved through regulated cell cycle events, such as the alternating activities of various D-type cyclins, cyclin-dependent kinases (CDKs), and E2F transcription factors. These cell cycle modulators and miRNA molecules are regulated during post-transcriptional modification[10,24]. The transcription factors Oct4, Sox2, and Nanog are also important for the self-renewal of pluripotent cells[7,25,26]. Oct4 and Nanog were the first transcription factors to be identified as necessary for the development and maintenance of ESC pluripotency. The expression of these factors is limited to pluripotent cell lines[26-28]. Additionally, Oct4, Sox2, and Nanog have an autoregulatory feedback loop, which is an important feature of human ESCs[29], and Sox2 implicitly interacts with Oct4[30].

Oct4, Sox2, and Nanog may be upstream regulators of the miR-302-367 cluster of miRNA, which have been identified and differentially expressed in human ESCs[31-33]. Conversely, miR-302-367 is required for Oct4, Sox2, and Nanog expression. Thus, miR-302-367 and the transcription factors (Oct4, Sox2, and Nanog) are tightly linked through an autoregulatory positive loop in pluripotent cells[34,35]. Additionally, miR-302a promotes the G_1/S transition by repressing the translation of cyclin D1 in human ESCs[36]. The inhibition of miR-302a causes an accumulation of pluripotent human ESCs in the G_1 phase[36]. ESCs usually have a rapid G_1/S transition, which results in an extremely rapid proliferation rate (-10 h) compared to that of differentiated cells (more than 18 h)[24]. The G_1/S transition is regulated by the cyclin D-Cdk4, 6 and cyclin E-Cdk2 complexes. The cyclin D-Cdk4, 6 complex is not present in mouse ESCs; however, the cyclin E-Cdk2 complex that induces S phase and DNA replication is present and active[20,37]. *In vivo* experiments performed in a developing lung demonstrated that miR-302-367 decreased the expression of inhibitors of *cdkn1a* (p21) and *Rbl2*, inhibitors of the cyclin E-Cdk2 complex, which resulted in the formation of an undifferentiated multi-layered lung endoderm[38]. Furthermore, in *Dicer*- and *Dgcr8*-knockout mice, ESCs exhibited reduced cell proliferation and an extended G_1 phase[18,19].

Similar to miR-302-367, the miR-290-295 cluster is highly expressed in mouse ESCs, is regulated by Oct4, and binds Oct4, Sox2, Nanog, and Tcf3 to its promoters[33,39]. The increased expression of the miR-290 family promotes the G_1/S transition, which enables rapid ESC proliferation and mediates the suppression of *cdkn1a*, *Rbl2*, and *Lats2*[37]. Indeed, the miR-290 family functionally antagonizes differentiation-related miRNAs, such as the let-7 family. The miR-290-295 cluster is rapidly downregulated during differentiation, which occurs with the restoration of let-7 maturation. Increased let-7 expression promotes differentiation by directly targeting pluripotency factors

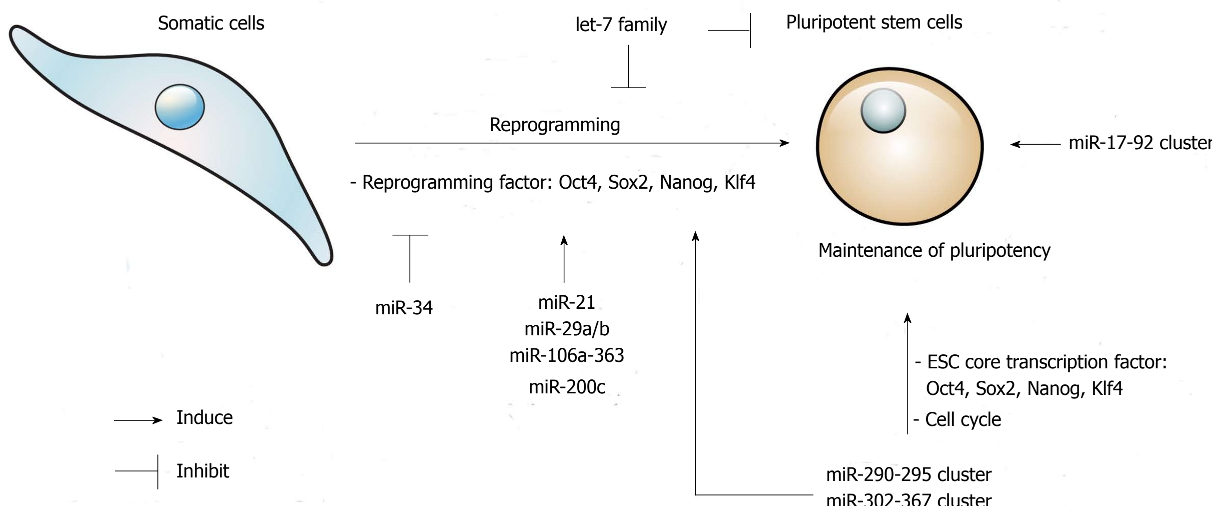

Figure 1 MicroRNAs regulate stem cell self-renewal and somatic cell reprogramming. ESC: Embryonic stem cell.

and ESC-enriched genes[40].

Another important gene in stem cell maintenance is c-Myc, which is inhibited by let-7[41]. In addition, c-Myc binds to the promoters of miR-141, miR-200, and miR-429. These miRNAs inhibit differentiation in mouse ESCs[42]. Furthermore, c-Myc stimulates the expression of the miR-17-92 cluster in tumor cells[43]. These miRNAs reduce the expression of the cell cycle control gene *Rb2*, which plays an important role in stem cell self-renewal[44]. Moreover, miR-92b promotes the G1/S transition through the repression of *cdkn1c* (p57, Kip2) in human ESCs[45]. In fact, the miR-302-367, miR-290-295, and miR-17-92 clusters have been designated as ESC-specific cell cycle-regulating miRNAs (ESCC miRNAs) because they promote the G1/S transition and cellular proliferation in ESCs[37].

Compared to their role in ESCs, there is less evidence for the involvement of miRNAs in the self-renewal of somatic stem cells. The overexpression of miR-205 enhanced proliferation and expanded the population of progenitor cells by modulating PTEN, a tumor-suppressor gene[46].

Therefore, stem cell self-renewal is tightly regulated through a complex network of core transcription factors, miRNAs, and the repression and/or promotion of differentiation mechanisms and pluripotent pathways, respectively (Figure 1).

MICRORNAS IN DIFFERENTIATION

Vascular differentiation: endothelial cells, vascular smooth muscle cells, and cardiomyocytes

Some studies indicate that miRNAs affect the vascular development or differentiation of stem cells, and others provide detailed reviews of the effect of miRNAs on endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and cardiomyocytes[47-49] (Figure 2).

Endothelial cell differentiation

The first evidence for the regulation of endothelial cell functions by miRNAs came from observations that dicer knockout mice displayed defects in embryos and yolk sacs during vasculogenesis and early angiogenesis[50]. Dicer, accompanied by the altered expression of vascular endothelial growth factor (VEGF), fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor; FLT1), kinase insert domain receptor (a type Ⅲ receptor tyrosine kinase; KDR), and tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (Tie-1), plays and essential role in endothelial development.

Increased expression of miR-126 was first identified in Flk-1$^+$ mesoderm populations derived from mouse ESCs[51]. Two additional studies, performed with zebrafish and mice, demonstrated that miR-126 is essential for vessel integrity and endothelial function regulation but that it is not required to control the differentiation of ESCs to ECs[52,53].

The expression of miRNAs associated with angiogenesis (let-7b, let-7f, miR-126, miR-130a, miR-133a, miR-133b, miR-210, and miR-296) was enhanced in day 10 differentiated cells compared to pluripotent human ESCs[54]. Increased expression of the let-7 family during differentiation occurred by directly targeting pluripotency factors and *ESC-enriched* genes[40]. Specifically, let-7f contributed to the angiogenic sprouting of ECs *in vitro*[55]. The other upregulated miRNAs, miR-130a, enhanced angiogenesis by modulating GAX (growth arrest-specific homeobox) and HOXA5 (homeobox protein Hox-A5), which are anti-angiogenic homeobox transcription factors[56]. Additionally, miR-210 was shown to be required for angiogenesis by targeting EphinA3[57], and miR-146b, miR-197, and miR-625 expression was enriched in CD31$^+$ endothelial populations derived from mouse ESCs[52]. Although the function of these miRNAs has been studied in cancer cells[58-60], their role in the differentiation and functionality of ECs remains unknown.

The miRNA miR-181a promotes the reprogramming of lymphatic ECs toward a blood vascular phenotype[61].

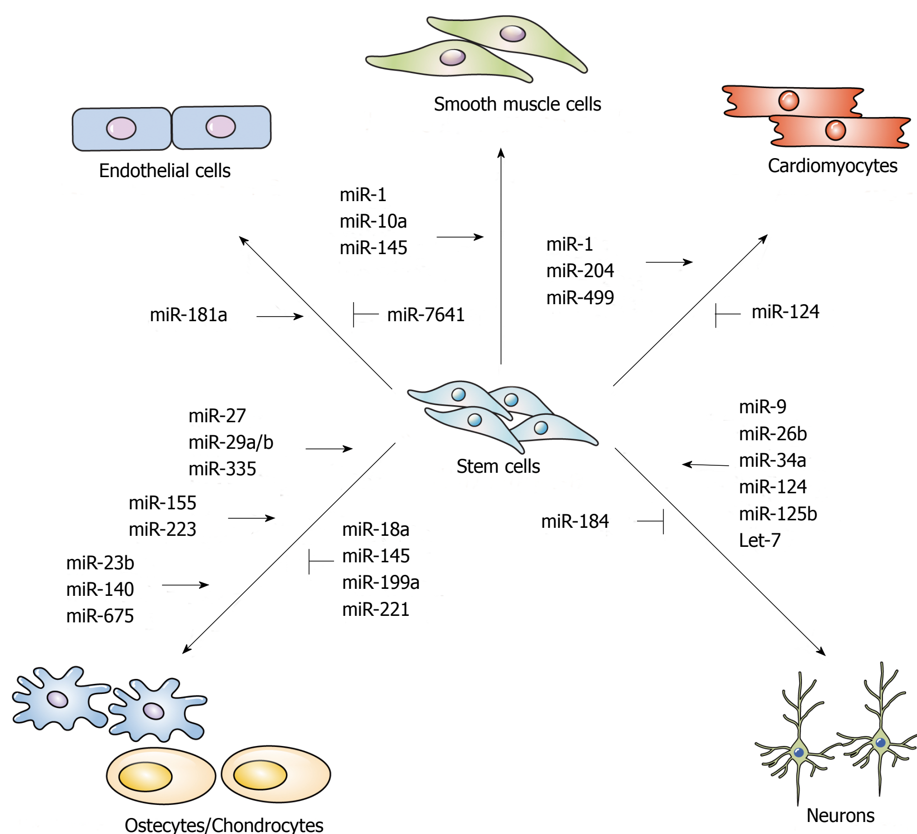

Figure 2 MicroRNAs are key regulators in stem cell differentiation.

The binding of miR-181a, to the 3'UTR of Prox1 (prospero homeobox 1, a key gene involved in lymphatic EC identity) results in inhibited expression. In human ESCs, miR-99b, miR-181a and miR-181b regulated the mRNA and protein expression of EC-specific markers, increased nitric oxide production, and improved therapeutic neovascularization *in vivo*[62]. In addition, the expression of miR-7641 was downregulated during the endothelial differentiation of human ESCs. The overexpression of this miRNA significantly suppressed the expression of CXCL1 (a member of the CXC chemokine family)[63]. CXCL1, which is involved in EC biogenesis and angiogenesis, is known to promote neovascularization by binding G-protein-coupled receptors[64,65].

Smooth muscle cell differentiation

The miRNAs miR-143 and miR-145 are abundantly expressed in smooth muscle tissue. These miRNAs promote smooth muscle cell (SMC) differentiation from neural crest stem cells and are upregulated during differentiation, which is consistent with early expression patterns in the aorta of developing mouse embryos[66-68]. Recently, it was discovered that miR-145 also promotes SMC differentiation from human ESCs[69]. The expression of miR-143 and miR-145 is controlled by serum response factor (SRF), myocardin (MYOCD), and the following miRNA target transcription factors: KLF4, ELK1, and angiotensin-converting enzyme (ACE)[66-68]. Other targets of miR-145 are Oct4, Sox2, and Klf4, which are transcription factors for the self-renewal of pluripotent cells. These miRNAs are involved in regulating cell fate decisions across different lineages[70]. A loss of miR-145 induced a different SMC phenotype, which was similar to the proliferating SMCs found in vascular lesions, but did not affect SMC differentiation[66,67]. A reduction in neointima formation after vessel injury was observed in miR-145$^{-/-}$mice and, to a lesser extent, in miR-143$^{-/-}$ mice[68]. However, the overexpression of miR-143 and miR-145 also decreased neointima formation in a rat model of acute vascular injury[71]. These data suggest that miR-143 and miR-145 are vital to SMC differentiation *in vitro*, but are not essential for SMC differentiation during embryonic development *in vivo*.

Another study showed that the increased expression of miR-10a during the *in vitro* differentiation of mouse ESCs to SMCs occurred via the post-transcriptional inhibition of histone deacetylase 4 (HDAC4)[72]. The inhibition of miR-10a impairs SMC differentiation.

The miRNA miR-1 is involved in cardiomyocyte differentiation, cardiac hypertrophy, and apoptosis; however, recent studies suggest that it also plays a role in SMC differentiation[73]. During the differentiation of mouse ESCs to SMCs, the expression of miR-1 steadily increased. Loss-of-function approaches using inhibitors against miR-1 resulted in the downregulation of SMC-specific markers and a decrease in the population of derived SMCs, indicating that miR-1 is required for the SMC lineage differentiation of ESC cultures. Previously identified

as a miR-145 target, KLF is a target for miR-1.

Cardiomyocyte differentiation

The miRNAs miR-1 and miR-133 were first described as critical regulators for muscle proliferation and skeletal muscle[74] and cardiac muscle[51] differentiation. Both miR-1 and miR-133 promote mesoderm formation from ESCs; however, these miRNAs have opposing functions during differentiation to cardiac muscle progenitors[51,74-76].

These miRNAs, miR-1-1 and miR-1-2, are specifically expressed in cardiac and skeletal muscle precursor cells and direct transcriptional targets, such as SRF, myogenic differentiation 1 (MyoD), and myocyte enhancement factor 2 (Mef2)[77]. An increased expression of miR-1 in mice led to embryonic developmental arrest at day 13.5, which resulted in a decreased population of proliferating ventricular cardiomyocytes[77]. Hand2, a transcription factor that regulates ventricular cardiomyocyte expansion, is a direct target of miR-1[77]. However, the targeted deletion of one of the two miR-1 genes (miR-1-2) located in muscle-specific miRNAs revealed numerous dysfunctions in the heart, including defective morphogenesis, electrical conduction, and unregulated cell-cycle control[76]. Additionally, *Drosophila melanogaster* miR-1 modulates cardiogenesis and muscle-gene expression[75]. Ivey *et al*[51] described that miR-1 acts as a repressor of non-muscle genes and that the overexpression of miR-1 upregulates Nkx2.5, an early cardiac marker, to promote cardiac differentiation. Notch ligand Delta-like 1 (Dll-1) is a target of miR-1[51]. In human ESC-derived embryoid bodies, miR-1 also increased the expression of myosin heavy chain (MHC) genes[78]. Additionally, miR-1 increased the expression of cardiomyocyte-specific genes and enhanced cardiomyocyte differentiation from human-derived cardiomyocyte progenitor cells by targeting HDAC4[79]. Interestingly, the transplantation of murine ESCs overexpressing miR-1 into the border zone of infarcted mouse hearts prevented ischemia-induced apoptosis[80]. In addition, miR-1 facilitates the electrophysiological maturation of ESCs[81]. Furthermore, when miR-1 was transfected into fibroblast cells, gene expression profiles shifted toward that of muscle-like cells[82]. Recently, miR-1 induced the expression of several cardiomyocyte markers, including Nkx2.5, GATA-4, cTnT, and CX43, *via* the downregulation of Hes-1, the downstream target molecule of the Notch pathway in MSCs[83].

Although miR-1 and miR-133 are bicistronic[76,84], they have opposing actions. The deletion of *miR-133a* genes causes lethal ventricular-septal defects, and results in the ectopic expression of smooth muscle genes. Therefore, miR-133a regulates the proliferation of cardiomyocytes by SRF and cyclin D2 activity[84]. Specific cardiac markers were downregulated in miR-133-overexpressed mouse and human ESCs[51,85], and miR-133 induced the proliferation of myoblasts by repressing SRF[74]. A recent study revealed that miR-133 inhibited the proliferation of the prostate cancer cell lines PC3 and DU145 by targeting the epidermal growth factor receptor (EGFR)[86]. Concurrently, our group also discovered that miR-133a expression increased during differentiation and that the overexpression of miR-133a promoted cardiac differentiation in human MSCs by targeting EGFR[87].

Increased miR-499 expression was discovered in adult cardiac progenitor cells and human ESCs[78,79]. This miRNA is encoded by an intron of MHC[88] and shares many predicted targets with miR-208, which plays a crucial role in the stress-adaptation of the adult heart. The overexpression of miR-499 reduced the proliferation and enhanced the differentiation of human cardiomyocyte progenitor cells and ESCs through targeting Sox6, which is expressed in heart and skeletal muscle[79]. The miRNA miR-499 has also been shown to play a role in myocyte lineage differentiation and the generation of mature working cardiomyocytes *in vitro* and after infarction *in vivo*[89]. Both Sox6 and regulator of differentiation 1 (Rod1) are targets of miR-499. In addition to ESCs, cardiac stem cells, and cardiomyocyte progenitor cells, a recent study showed that the overexpression of miR-499 in rat MSCs induced cardiac differentiation through the Wnt/β-catenin signaling pathway[90].

Additionally, miR-204 is required for human cardiomyocyte progenitor cell differentiation, which occurs through targeting ATF-2[91], whereas miR-124 inhibits the cardiomyocyte differentiation of MSCs by targeting STAT3[92]. Finally, the deletion of the miR-17-92 cluster led to very specific defects in the development of the heart[93]; however, the function of the miR-17-92 cluster in cardiac differentiation and development remains unclear.

Neuronal differentiation

Neural stem cells (NSCs) give rise to neurons, astrocytes, and oligodendrocytes and play an important role in embryonic development and the maintenance of the adult central nervous system (CNS)[94]. The differentiation of NSCs is tightly associated with multiple signaling pathways: the Wnt signaling pathway regulates NSC proliferation and differentiation[95], the transcription factors Neurog2 and Tbr2 are linked to NSC differentiation[96]; the orphan nuclear receptor TLX is necessary for adult NSC proliferation[97]; and the methyl CpG binding protein 2 (MeCP2), methyl-CpG binding protein 1 (MBD1), and histone-lysine N-methyltransferase Ezh2 are related to adult neurogenesis[98,99]. In the mammalian brain, some miRNAs expression is tissue-specific, such as the let-7 family, miR-124, and miR-9, which regulate neurogenesis[100,101]. Brain-specific miR-124 is upregulated during CNS development and the neuronal differentiation of the adult subventricular zone (SVZ)[102,103]. During neurogenesis, the suppression of RE-1-silencing transcription repressor (REST) induces the expression of miR-124, which represses JAG1, Dlx2, and Sox9. In addition, laminin γ1 and integrin β1, which are expressed in neural progenitors but inhibit neuronal differentiation, are also targeted by miR-124 and lead to neurogenesis[104]. The miRNA miR-9 is also highly expressed in the brain and is involved in modulating the balance between

NSC self-renewal and differentiation *via* negative TLX expression[105]. The overexpression of miR-9 promotes neural differentiation but downregulates TLX. Let-7d, a member of the let-7 family, also targets TLX, promotes neurogenesis, and reduces NSC proliferation[106]. Let-7a is a downstream molecule of tripartite motif-containing protein 32 (TRIM32); therefore, let-7a is also required to induce NSC differentiation[107]. The overexpression of TRIM32 induces neuronal differentiation, whereas the inhibition of TRIM32 preserves the self-renewal capability of neural progenitor cells. The miRNA miR-137 is essential for embryonic NSC fate decisions; the overexpression of miR-137 inhibits NSC proliferation and induces accelerated differentiation by suppressing histone lysine-specific demethylase 1 (LSD1), a co-transcription factor of TLX[108]. Additionally, miR-137, which mediates epigenetic proteins such as MeCP2 (a DNA methyl-CpG-binding protein), Ezh2, and Polycomb group (PcG) protein, regulates the balance of NSC proliferation and differentiation in adult neurogenesis. A reduction of miR-137 expression promotes differentiation, whereas the overexpression of miR-137 increases adult NSCs proliferation[98]. Similar to miR-137, miR-184 is associated with controlling the balance between the proliferation and differentiation of adult NSCs. Upregulated miR-184 targets methyl-CpG binding protein 1 (MBD1) and Numblike (Numbl), which are related to NSC differentiation in the adult brain, to induce cell proliferation and reduce the differentiation of adult NSCs[99]. In neural stem/progenitor cells (NSPCs) isolated from adult mice, the miR-106b-25 cluster (miR-106b, miR-93, and miR-25) regulates NSPC proliferation and differentiation. The miRNA miR-25 targets insulin/insulin-like growth factor-1 (IGF) signaling pathways. The expression of miR-106b-25 is mediated by FoxO3, a member of the FoxO family of transcription factors that is important for the maintenance and differentiation of NSCs[109]. Recently, it was determined that miR-34a is involved in NSC differentiation; miR-34a promotes Notch signaling by repressing Numbl, a negative regulator of Notch signaling that inhibits neuronal differentiation[110]. Additionally, miR-26b activates neurogenesis by suppressing Ctdsp2 protein expression[111,112]. By targeting Nestin, miR-125b promotes NSPC differentiation and migration while inhibiting NSPC proliferation[113] (Figure 2).

Osteoblast, osteoclast, and chondrocyte differentiation

The skeleton consists of osteoblasts and osteoclasts in bone tissue and chondrocytes in cartilage tissue[114]. Increasing evidences suggests that miRNAs are an integral part of regulating bone and cartilage formation, metabolism, homeostasis, osteogenesis, and chondrogensis[115,116].

Osteoblast differentiation from bone marrow stromal cells undergoes three stages: pre-osteoblast (proliferation), osteoblast/pre-osteocyte (matrix maturation), and osteocyte (mineralization)[117]. Each cell type expresses different genes and factors; therefore, miRNAs may be selectively expressed in particular stages during osteogenesis. At different stages of osteoblast differentiation, miR-29 has multiple distinct functions. For example, miR-29b initiates the osteogenic pathway by repressing anti-osteogenic factors, such as HDAC4, TGF-β3, activin A receptor type IIA (ACVR2A), beta-catenin-interacting protein 1 (CTNNBIP1), and dual-specific phosphatase (DUSP2). Collagen type I (COL1A1) directly targets miR-29b. During mineralization, when collagen accumulation is at a steady state, high endogenous levels of miR-29b downregulation the mRNA expression of COL1A1[118]. In addition, miR-29 suppresses osteonectin (secreted protein acidic and rich in cysteine, SPARC) during matrix maturation and the mineralization phase during late differentiation[119]. Although collagens and osteonectin play an important role in bone mass and osteogenesis, the inhibition of these proteins by miR-29b prevents sclerotic bone formation and increases bone structure stability[117]. Moreover, canonical Wnt signaling is involved in osteoblast differentiation; a high level of β-catenin is required for osteogenesis. Therefore, targeting the Wnt pathway by miRNAs has been shown to contribute to osteogenesis[120]. The miR-29 family also targets Wnt signaling-mediated proteins; the expression of miR-29 is increased by Wnt activation during osteoblast differentiation. Additionally, miR-29a negatively regulates the Wnt receptor complex Dickkopf-related protein 1 (Dkk1), Kremen2, and secreted frizzled related protein 2 (sFRP2)[121], whereas miR-29b downregulates the β-catenin inhibitor CTNNBIP1[118]. Both miR-27 and miR-335 are upregulated during osteogenesis and target the APC gene and Dkk1, a negative regulator of Wnt signaling, respectively, which leads to osteoblast differentiation[122,123].

Only a few miRNAs contribute to osteoclast differentiation. In particular, miR-223 is regulated by transcription factor PU.1. An increased expression of miR-223 and receptor activator of nuclear factor-κB (RANK) is observed in bone marrow derived osteoclast precursors after induction by M-CSF[124]. miR-223 regulates NFIA, a suppressor of osteoclastogenesis, which leads to the upregulation of the M-CSF receptor[125]. A key regulator in the maturation of hematopoietic cells to macrophages, miR-155 has been studied as another osteoclastogenic miRNA[126]. miR-155 represses MITF, a necessary transcription factor for osteoclast differentiation, to inhibit osteoclastogenesis[127].

Cartilages tissue forms bone *via* the endochondral process of ossification. The loss of miRNAs in cartilage accelerates the differentiation of mature hypertrophic chondrocytes and abnormal bone growth[128]. Cartilage-specific miR-140[129] is related to palatogenesis, which mediates platelet-derived growth factor D (PDGFD) signaling in zebrafish[130], craniofacial development and endochondral bone formation *via* targeting HDAC4[131] and inhibits BMP signaling in mouse models[132]. HDAC4 and BMP signaling pathways contribute to chondrocyte hypertrophy and osteoblast differentiation and can be negative effector of osteogenesis. The miRNA miR-675 can promote chondrogenic differentiation by inducing the

expression of cartilage-specific collagen type Ⅱa through the positive regulation of cartilage-specific Sox9[133]. The chondrogenic differentiation of MSCs is induced by miR-23b, which negatively inhibits of protein kinase A signaling[134]. In addition, miR-18a, miR-199a, miR-145, and miR-221 have been identified as negative regulators of chondrogenesis. To repress chondrogenesis, miR-18a directly targets the CCN family protein 2/connective tissue growth factor (CCN2/CTGF)[135]. Similarly, miR-199a, a bone morphogenic protein 2-responsive miRNA, significantly inhibits early chondrogenesis by targeting Smad1[136]. In addition, miR-145 targets Sox9, a key transcription factor for chondrogenic differentiation[137,138], and miR-221 negatively regulates Mdm2 and therefore prevents the degradation of Slug protein, which is involved in chondrogenesis inhibition[139] (Figure 2).

Other types of differentiation

Despite the multi-lineage differentiation potential of stem cells, little is known about the differentiation of stem cells to other cell types than those described above. For example, the hepatic differentiation of human umbilical cord lining-derived MSCs (hUC-MSCs) and liver-derived progenitor cells (LDPCs) is regulated by miR-542-5p and miR-146a[140]. The miRNA miR-182 is involved in the differentiation of inner ear stem/progenitor cells into hair-like cells *via* the repression of Tbx1[141]. Pancreatic transcription factor Ptf1a is specifically expressed at different stages during pancreatic development; low levels of Ptf1a enhance the differentiation of pancreatic progenitor cells to endocrine cells, whereas high levels of Ptf1a are involved in exocrine cell differentiation. The endogenous expression of Ptf1a is regulated by miR-18a[142]. During the adipogenic differentiation of mouse ESCs, the expression of miR-10b, miR-15, miR-26a, miR-30a-5p, miR-30c, miR-98, miR-99a, miR-103, miR-143, miR-148a, miR-152, miR-224, miR-422b, and miR-let-7b increased, whereas the expression of the miR-17-92 cluster was downregulated[143]. Myeloid differentiation is promoted by PU.1 transcription factor, and the overexpression of the miR-23a cluster in hematopoietic progenitor cells suppresses B-cell development[144]. Furthermore, miRNAs are involved in the differentiation of diploid spermatogonia to haploid spermatozoa. The miRNA miR-34c is highly expressed in the late stages of spermatogenesis, which induces the upregulation of germ cell-specific genes[145].

MICRORNAS IN REPROGRAMMING

In 2006, the astonishing research of Yamanaka demonstrated that somatic cells such as mouse fibroblasts, can be reprogrammed to a pluripotent state using only four transcription factors: Oct4, Sox2, Klf4, and c-Myc[5]. These reprogrammed fibroblasts are referred to as iPSCs, and they are functionally and molecularly similar to ESCs. After one year, the same group induced human iPSCs in a similar manner as the mouse iPSCs[146]. These initial studies introduced the somatic cell reprogramming strategy. Although the method of transcription factor-mediated reprogramming is simple, problems such as time, low efficiency, and the possibility of tumorigenesis remain unsolved[147]. To improve the quality of generated iPSCs, researchers have focused on using miRNAs, which are associated with regulating the epigenome. Because the ectopic expression of transcription factors during reprogramming is related to epigenetic changes, miRNAs are considered an attractive alternative for somatic cell reprogramming[35] (Figure 1).

To improve the efficiency of iPSC generation, reprogramming barriers must be overcome. The reprogramming process undergoes two phases: the early phase (initiation phase) and the late phase[8]. The early phase is a pre-pluripotent state involving increased cell proliferation and a change into an epithelial-like cellular state called the mesenchymal-epithelial transition (MET)[148]. This phase is regulated by p53-induced cell-cycle repression and the TGF-β-accelerated epithelial-mesenchymal transition (EMT). The late phase is the transition of pre-iPSCs by inducing pluripotency-related genes, such as Nanog, Sox2, and Lin28, and establishing the pluripotency network[8]. Thus, reducing these barriers by utilizing miRNA-mediated epigenetic and transcriptional regulation enhances reprogramming efficiency and generates functional cells that resemble ESCs[8,148,149].

The first attempt to reprogram focused on miRNAs that were highly expressed in ESCs and governed pluripotency but were absent in fibroblasts. Among members of the miR-290-295 family, miR-291-3p, miR-294, and miR-295, in combination with Oct4, Sox2, and Klf4, increased the reprogramming efficiency of mouse fibroblasts[150]. In human somatic cells, miR-302a-367 and/or miR-371-373 (mouse homolog miR-290-295), in combination with Oct4, Sox2, Klf4, and c-Myc, enhanced the efficiency of reprogramming by inhibiting TGF-β-induced EMT[151]. During the early reprogramming stage, miR-17-92, miR-106b-25, and miR-106a-363 clusters, which share the seed sequences of the miR-302 cluster, were shown to be highly induced[152]. The overexpression of the miR-106a-363 and miR-302-367 clusters promoted a distinct increase in iPSCs generated from mouse fibroblasts. This increase was achieved by targeting TGF-β type Ⅱ receptor with Sox2, Klf4, and Oct4, which accelerated MET[153]. In addition, the activation of BMP signaling induced the expression of the miR-205 and miR-200 family and enhanced the MET[154]. Therefore, the TGF-β and BMP signaling pathways are critical mechanisms that induce MET and promote reprogramming. Further investigation of somatic reprogramming is possible using only miRNAs to directly promote reprogramming events. Recently, Anokye-Danso and coworkers reported that the transfection of miR-302 and miR-367 clusters successfully reprogramed mouse and human somatic cells to iPSCs without the use of exogenous transcription factors[155]. Interestingly, the direct transfection of mature biomimetic miRNAs, such

Table 1 Small molecules in stem cell fate and somatic cell reprogramming

Chemical	Effect (Target)	Result	Ref.
PD0325901 CHIR9902	MEK inhibitor GSK-3 inhibitor	Promotes mouse ESC self-renewal	[161]
Y27632 Thiazovivin	ROCK inhibitor	Enhances human ESC survival	[161-164]
SB431542	TGF-β receptor inhibitor (SMAD signaling inhibitor)	Induces human ESC differentiation into endothelial cells and neural tissues	[167,168]
VPA BIX-01294 RSC133 5-Aza SB431542 PD0325901	HDAC inhibitor HMT inhibitor DNMT inhibitor TGF-β receptor inhibitor MEK inhibitor	Somatic cell reprogramming	[170-175]
TSA Trapoxin Chlamydocin SR1 PGE2	HDAC inhibitor AHR antagonist PG pathway	Promote HSC self-renewal	[177-179]
Pyrvinium SKL2001	Wnt inhibitor	Promote MSC self-renewal	[191,192]
H-89 Katogenin	PKC inhibitor Filamin A	Induces human MSC differentiation into chondrocytes	[130,180]
Purmorphamine CW008	RUNX2 activator cAMP/PKA/CREP pathway agonist	Induces human MSC differentiation into osteoblasts	[181,182]
SJA710-6		Induces rat MSC differentiation into hepatocytes	[183]
PMA	PKC activator	Induces rat MSC differentiation into cardiomyocytes	[184,185]
LY294002 CHIR9902	PI3K/AKTinhibitor GSK-3 inhibitor	Inhibits mouse MSC differentiation into adipocytes	[186,187]
Troglitazone	PPARγ agonist	Induces human MSC differentiation into adipocytes	
SB431542 LY94002	SMAD inhibitor PI3K/AKT inhibitor	Induces human MSC differentiation into neural-like cells	[188-190]

ESC: Embryonic stem cell; HSC: Hematopoietic stem cell; MSC: Mesenchymal stem cell; MEK: Mitogen-activated protein kinase kinase; GSK-3: Glycogen synthase kinase 3; ROCK: Rho-associated protein kinase; TGF-β: Transforming growth factor beta; HDAC: Histone deacetylases; HMT: Histone methyltransferases; DNMT: DNA methyltransferases; AHR: Aryl hydrocarbon receptor; PG: Prostaglandins; PKC: Protein kinase C; RUNX2: Runt-related transcription factor 2; cAMP: Cyclic adenosine monophosphate; CREP: cAMP response element-binding protein; PI3K: Phosphoinositide 3 kinase; AKT: Protein Kinase B; PPARγ: Peroxisome proliferator-activated receptor gamma.

as miR-200c and the miR-302-369 family, promoted the reprogramming of mouse and human somatic cells. This method does not require lentiviral vectors for gene transfer[156].

Contrary to the aforementioned examples, some miRNAs must be suppressed to enhance reprogramming. For example, let-7 miRNAs are negative regulators of the potent reprogramming factor Lin28. The inhibition of let-7 miRNAs leads to the dedifferentiation of somatic cells to iPSCs, which induces cell proliferation and pluripotency genes[40]. Another important miRNA barrier for reprogramming is the p53-mediated pathway. The p53-mediated pathway induces the expression of the miR-34 family and the suppression of the pluripotency factors Nanog and Sox2[157]. The genetic deletion of miR-34a increased the efficiency and kinetics of reprogramming and established pluripotency at a late stage. Additionally, the suppression of p53, by overexpressing miR-138[158] or repressing miR-21 and miR-29a, enhanced reprogramming[159]. The expression of endogenous miRNAs is regulated by transcription factors[160]. The expression of miR-29b is directly regulated by Sox2 during iPSC generation and miR-29b is an essential facilitator for Oct4, Klf4, Sox2, and c-Myc (or Oct4, Klf4, and Sox2) mediated reprogramming[161].

Reported reprogramming factors Oct4, Klf4, Sox2, and c-Myc have demonstrated that miRNAs play a crucial role in regulating stem cell fate events, such as reprogramming, differentiation, and self-renewal. However, some questions pertaining to the mechanisms of reprogramming remain unresolved. Addressing these questions will provide further understanding of reprogramming and will promote the development of iPSC generation technologies and stem cell therapies.

SMALL MOLECULES AND STEM CELL FATE

Stem cell fate is regulated by both intrinsic/extrinsic regulators and the extracellular niche. Because these regulators have limitations, such as efficiency and selectivity for controlling stem cell fate, a new strategy is to use of small molecules[162] (Table 1). Compared to genetic manipulations, small-molecule approaches have a number of advantages: 1) the biological effects of small molecules are rapid, reversible, and dose-dependent; 2) small molecules have specific targets in signaling pathways or epigenetic mechanisms; and 3) a variety of chemical libraries provide data for the functional optimization of small molecules[163]. Recently, many small molecules have been identified and characterized that can manipulate stem cell fate, including self-renewal, lineage-specific differentiation, and somatic cell reprogramming[35,164].

The self-renewal capacity of mouse ESCs is maintained by PD0325901 (MEK inhibitor) and CHIR99021 (GSK3 inhibitor) without feeder cells or exogenous cytokines[165]. The molecules Y-27632 and thiazovivin (ROCK inhibitor) enhance the survival of human ESCs[166-168], whereas a combination of PD0325901, CHIR99021, and Y-27632 supplemented with bFGF supports the maintenance of human ESCs[169]. Because the lineage-specific commitment of stem cells provides possible therapeutic applications, studies that control stem cell differentiation have been consistently reported.

Wnt signaling modulators promote cardiomyocyte generation in zebrafish embryos and murine ESCs[170], and the inhibition of TGF-β receptor by SB431542 induces the endothelial cell differentiation of human ESCs[171]. The inhibition of SMAD signaling by noggin and SB431542 directs the differentiation of human ESCs to neural tissues[172].

ESCs have the ability to propagate indefinitely and to differentiate into any cell type; however, ethical issues regarding the use of ESCs still remain. Therefore, tissue-specific adult stem cells and the ability to reprogram somatic cells have fascinated researchers[164,173]. Ever since Yamanaka demonstrated that Oct4, Sox2, Klf4, and c-Myc can convert mouse fibroblasts into induced pluripotent stem cells (iPSCs)[5], the study of reprogramming has accelerated with the use of epigenetic process modulators, which target histone deacetylase (HDAC)[174,175], histone acetyltransferase (HMT)[176,177], and DNA methyltransferase (DNMT)[176,178]. Recently, a chemical cocktail including HDAC inhibitors and other kinase inhibitors enhanced the reprogramming efficiency of human fibroblasts[175,179].

Hematopoietic stem cells (HSCs) are related to the hematopoietic lineage, and cell phenotypes include macrophages, erythrocytes, dendritic cells, T-cells, B-cells, and NK-cells[180]. The fate of HSCs is regulated by small molecules that promote self-renewal[181-183]. Using small molecules, multipotent MSCs can differentiate into various non-hematopoietic cells, such as chondrocytes[134,184], osteoblasts[185,186], hepatocytes[187], cardiomyocytes[188,189], adipocytes[190,191] and neuronal-like cells[192-194]. Additionally, the maintenance of MSCs is associated with the Wnt signaling pathway[195,196].

Although chemical approaches are a very young field in stem cell research, these small molecules exhibit a similar biological outcome to that achieved with the use of miRNAs in stem cell fate regulation[35]. Recently, small molecules have been correlated with endogenous miRNA expression and function[197-202]. Therefore, identifying the relationship between miRNAs and small molecules could provide new insights for drug development for regenerative medicine and elucidate detailed mechanisms of miRNA expression and function in the control of stem cell fate.

CONCLUSION AND FUTURE DIRECTIONS

Increasing evidence has demonstrated that miRNAs are promising regulators of stem cell fate. The current strategy in stem cell biology can elucidate the links between miRNAs and stem cell fate determination. Although miRNAs strictly regulate the multiple molecular signaling pathways and transcription factors that control stem cell fate, some significant issues have not received adequate attention. Current challenges focus on verifying the downstream targets of miRNA; however, the study of miRNA upstream targets is virtually nonexistent. In addition, the correlation between miRNAs is not well understood. Small molecules not only modulate stem cell fate but also regulate miRNA synthesis and the function of transcription factors and miRNAs. The challenge of identifying the relationship between miRNAs and small molecules is still at an initial stage. Complementary to conventional and interdisciplinary strategies, including miRNAs and/or chemical manipulation techniques in the regulation of stem cell self-renewal, tissue- or organ-specific differentiation, and iPSC generation provides a powerful tool to identify the underlying cellular mechanisms of stem cell biology and isolate the therapeutic agents required for clinical applications such as cell therapy and regenerative medicine.

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