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**MicroRNAs as novel regulators of stem cell fate**

**Choi E *et al.***MicroRNAs in stem cell fate

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**Abstract**

Mounting evidence in stem cell biology showed that microRNAs (miRNAs) play a crucial role in cell fate specification, including stem cell self-renewal, lineage-specific differentiation, and somatic cell reprogramming. This is tightly regulated by specific gene expression patterns that involve miRNAs and transcription factors. To maintain stem cell pluripotency, specificmiRNAs suppress transcription factors that promote differentiation, whereas for differentiation to begin, lineage-specific miRNAs are up-regulated *via* inhibiting transcription factors that promote self-renewal. Small molecules can be used in a similar manner as natural miRNAs to regulate stem cell fate, and a number of natural and synthetic small molecules have been used to regulate cell fate. The strategy to identify miRNAs as a novel regulator of stem cell fate will provide insight into stem cell biology, and aid in understanding the molecular mechanisms and the crosstalk between miRNAs and in stem cells. Ultimately, significant advances in regulating stem cell fate will contribute to effective medical therapies for tissue repair and regeneration. This review summarizes the current insights into stem cell fate determinants by miRNAs, focusing on stem cell self-renewal, differentiation, and reprogramming. Small molecules for control of 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 responsible for regenerative medicine, due to the capacity of stem cells for self-renewal and differentiation into specific cell types. MicroRNAs (miRNAs) are short non-coding RNAs, which negatively regulate gene expression at the post-transcriptional level. Recent studies suggest that miRNAs are key molecules in stem cell fate decisions, and such regulation is manifested as fine tuning cell- and tissue-specificity of gene expression. This review summarizes the current insights into stem cell fate determinants by miRNAs, focusing on stem cell self-renewal, differentiation, and reprogramming. Small molecules for control of stem cell fate are also highlighted.

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**INTRODUCTION**

Stem cells are a potential source for regenerative medicine and tissue engineering. They have the dual capacity to both self-renew and differentiate into multiple disparate cell lineages[[1](#_ENREF_1),[2](#_ENREF_2)]. These cells can be classified into embryonic stem cells (ESCs), nonembryonic adult stem cells and induced pluripotent stem cells (iPSCs). ESCs are pluripotent cells produced from 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](#_ENREF_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](#_ENREF_4)]. Adult stem cells are multipotent; they can produce a limited number of differentiated cell types of their specific tissue of origin. iPSCs are reprogrammed to be embryonic-like stem cells from adult somatic cells[[5](#_ENREF_5),[6](#_ENREF_6)].

A determinant of stem cell fate is controlled by transcription factors, epigenetic regulation, and non-coding RNAs[[7](#_ENREF_7),[8](#_ENREF_8)]. Transcription factors are well-known for regulation of gene expressions by directly or indirectly binding DNA elements, and epigenetic regulation including 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 decision, including maintenance and differentiation of stem cells[[7](#_ENREF_7),[9](#_ENREF_9)].

MicroRNAs (miRNAs) are single-stranded, small non-coding RNA molecules. miRNAs modulate gene expression by either inhibiting mRNA translation or inducing mRNA degradation, resulting from incompletely or completely binding to the 3’ untranslated region (3’ UTR) of specific mRNAs[[10](#_ENREF_10),[11](#_ENREF_11)]. About more than 1000 different mature miRNAs have been discovered in humans, and they regulate one third of all protein-coding genes[[12](#_ENREF_12),[13](#_ENREF_13)]. Computational prediction of miRNA targets, functions, and expression, is 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](#_ENREF_14),[15](#_ENREF_15)]. One miRNA can target a large number of mRNAs and/or many miRNAs can bind to one specific mRNAs This may result in miRNAs mediating powerful effects in biological process, 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](#_ENREF_16),[17](#_ENREF_17)]. Many studies showed that enzymes involved in miRNA processing and maturation, using deletion of Dicer or Dgcr8, miRNAs are important in ESCs pluripotency maintenance and differentiation[[18-20](#_ENREF_18)]. miRNAs also play a role in differentiation and self-renewal of mesenchymal stem cells (MSCs)[[21](#_ENREF_21)]. Excessive observations suggest that miRNAs critically regulate stem cell fate, including self-renewal and differentiation into specific lineages, and reprogramming. Thus, this review focuses on miRNAs as powerful regulators of stem cell fate. Furthermore, we discussed about the potential regulation of small molecules for 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. For self-renewal to occur, stem cells must undergo proliferation without differentiation and apoptosis, and maintain the undifferentiated state[[22](#_ENREF_22),[23](#_ENREF_23)].

Cell division for self-renewal is achieved through regulated events of cell cycle, including the alternating activities of various D-type cyclins, cyclin-dependent kinases, and E2F transcription factors. These cell cycle modulators are regulated during post-transcriptional modification, including miRNAs[[10](#_ENREF_10),[24](#_ENREF_24)]. Three transcription factors Oct4, Sox2, and Nanog are also important for the pluripotent cell self-renewal[[7](#_ENREF_7),[25](#_ENREF_25),[26](#_ENREF_26)]. Oct4 and Nanog were the first transcription factors to be identified as a necessity for development and pluripotency maintenance in ESCs. The expression of these factors are limited to pluripotent cell lines[[26-28](#_ENREF_26)], and Sox2 interact with Oct4[[29](#_ENREF_29)]. Oct4, Sox2, and Nanog have autoregulatory feedback-loop, and this regulation is an important feature of human ESCs[[30](#_ENREF_30)].

Oct4, Sox2, and Nanog may be upstream regulators of miR-302-367 promoter, and these miRNA clusters were identified and differentially expressed in ESCs[[31-33](#_ENREF_31)]. Conversely, miR-302-367 is required for Oct4, Sox2, and Nanog expression. Taken together, miR-302-367 and pluripotent factors (Oct4, Sox2, and Nanog) are tightly linked through autoregulatory positive loop in pluripotent cells[[34](#_ENREF_34),[35](#_ENREF_35)]. miR-302a promotes G1/S transition by translationally repressing cyclin D1 in human ESCs[[36](#_ENREF_36)]. Inhibition of miR-302a accumulate cells of G1 phase in pluripotent human ESCs[[36](#_ENREF_36)]. ESCs have a usually rapidly G1/S transition, resulting in an extremely fast proliferation rate (10 h) compared to differentiated cells (more than 18 h)[[24](#_ENREF_24)]. The G1/S transition is regulated by cyclin D-Cdk4, 6 and cyclin E-Cdk2 complexes. In mouse ESCs, the cyclin D-Cdk4,6 complex is not present, while the cyclin E-Cdk2 complex is present and active, which induces S phase and DNA replication[[20](#_ENREF_20),[37](#_ENREF_37)]. *In vivo* experiments in the developing lung showed that miR-302-367 decreased the expression of inhibitors of cyclin E-Cdk2 complex, *cdkn1a* (p21), *Rbl2*, resulting in the formation of an undifferentiated multi-layered lung endoderm[[38](#_ENREF_38)]. Furthermore, Dicer- or Dgcr8-knockout mice represented that proliferation was slow and G1 phase was accumulated in ESCs[[18](#_ENREF_18),[19](#_ENREF_19)].

Similar to miR-302-367, the miR-290-295 cluster is highly expressed in ESCs, and its promoters are occupied by Oct4, Sox2, Nanog, and Tcf3, and is dependent on Oct4[[33](#_ENREF_33),[39](#_ENREF_39)]. The high level of miR-290 family promotes the G1/S transition, enabling rapid proliferation of ESCs while mediating suppression of *cdkn1a*, *Rbl2*,and *Lats2*[[37](#_ENREF_37)]. Indeed, miR-290 family functionally antagonizes differentiation-related miRNAs, such as the let-7 family. During differentiation, miR-290-295 cluster is rapidly downregulated, coincident with restoration of let-7 maturation, and increased let-7 expression promotes differentiation by directly targeting pluripotency factors and ESC-enriched genes[[40](#_ENREF_40)].

*c-Myc*, another important gene in stem cell maintenance, is inhibited by let-7[[41](#_ENREF_41)]. In addition, *c-Myc* is bound to the promoter of the miR-141, miR-200, and miR-429. These miRNAs inhibits differentiation in mouse ESCs[[42](#_ENREF_42)]. *c-Myc* also stimulates expression of miR-17-92 cluster in tumor cells[[43](#_ENREF_43)]. These miRNAs reduced cell cycle control gene, *Rb2*, which plays an important role in stem cell self-renewal[[44](#_ENREF_44)]. Moreover, miR-92b promotes *G1/S* transition through repression of *cdkn1c* (p57, Kip2) in human ESCs[[45](#_ENREF_45)]. Because, *G1/S* transition and cellular proliferation is promoted by miR-302-367 cluster, miR-290-295 cluster and miR-17-92 cluster in ESCs, these miRNAs were denoted as the ‘ESCC miRNAs’ ES cell-specific cell cycle-regulating miRNAs[[37](#_ENREF_37)].

Compared to their role in ESCs, evidence for the involvement of miRNAs in the self-renewal of somatic stem cells is less. *miR-205* overexpression expanded the progenitor population and enhancing proliferation by modulation PTEN, known as tumor suppressor gene[[46](#_ENREF_46)].

Therefore, stem cell self-renewal is tightly regulated through a complex network of core transcription factors and miRNAs, combined with repression of differentiation programs and promotion of pluripotent programs (Figure 1).

**MICRORNAS IN DIFFERENTIATION**

***Vascular differentiation***

There are some studies that indicate that miRNAs affect vascular development or differentiation from stem cells, while others reported detailed reviews for endothelial cells (ECs), vascular smooth muscle cells, and cardiomyocytes[[47-49](#_ENREF_47)] (Figure 2).

***Endothelial differentiation***

The first evidence for the regulation of endothelial cell functions by miRNAs came from the observations that dicer knockout mice induced defects in vasculogenesis and early angiogenesis in embryos and yolk sacs[[50](#_ENREF_50)]. Dicer plays an essential role in development of endothelium, accompanied by altered expression of vascular endothelial growth factor, fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor), kinase insert domain receptor (a type III receptor tyrosine kinase), and tyrosine kinase with immunoglobulin-like and EGF-like domains 1, (Tie-1).

miR-126 was first identified as enriched in Flk-1 mesoderm populations derived from mouse ESCs[[51](#_ENREF_51)]. Two additional studies demonstrated that miR-126 is essential in the regulation of vessel integrity and endothelial function, but did not control differentiation of ESCs to ECs in zebrafish and mice[[52](#_ENREF_52),[53](#_ENREF_53)].

In day 10 differentiated cells compared to pluripotent hESCs, the expression of miRNAs associated with angiogenesis (let-7b, 7f, miR-126, 130a, 133a, 133b, 210, and 296) was induced[[54](#_ENREF_54)]. let-7 family members were augmented during differentiation by directly targeting pluripotency factors and ESC-enriched genes[[40](#_ENREF_40)]. Especially, let-7f contributed to angiogenic sprouting of ECs *in vitro*[[55](#_ENREF_55)]. The other upregulated miRNAs, miR-130a, augmented angiogenesis by modulating growth arrest specific homeobox and homeobox protein Hox-A5, which is an anti-angiogenic homeobox transcription factors[[56](#_ENREF_56)]. miR-210 was also shown to be required for angiogenesis by targeting EphinA3[[57](#_ENREF_57)]. miR-146b, miR-197, and miR-625 were enriched in CD31+ endothelial population derived from mouse ESCs[[52](#_ENREF_52)]. Function of these miRNAs was studied in cancer cells[[58-60](#_ENREF_58)]. However, their function in differentiation and function of ECs is unknown.

It has been reported that miR-181a promoted the reprogramming of lymphatic endothelial cells toward a blood vascular phenotype[[61](#_ENREF_61)]. miR-181a binds 3’UTR of Prox1 (prospero homeobox 1, a key gene involved in lymphatic endothelial cell identity), resulting in expression inhibition. In human ESCs, miR-99b, miR-181a, and miR-181b potentiated the mRNA and protein expression of EC-specific markers, increased nitric oxide production, and improved therapeutic neovascularization *in vivo*[[62](#_ENREF_62)]. In addition, the expression of miR-7641 was downregulated during endothelial differentiation from human ESCs, and overexpression of this miRNA significantly suppressed CXCL1 (a member of the CXC chemokine family) expression[[63](#_ENREF_63)]. The CXCL1 is known to promote neovascularization by binding G-protein coupled receptors and is related to ECs biogenesis such as angiogenesis[[64](#_ENREF_64),[65](#_ENREF_65)].

***Smooth muscle differentiation***

miR-143 and miR-145 is abundantly expressed in smooth muscle, promotes SMC differentiation from neural crest stem cells, and is upregulated during differentiation, consistent with the early patterns found in the aorta of developing mouse embryos[[66-68](#_ENREF_66)]. Recently, it was found that miR-145 also promotes SMC differentiation from human ESCs[[69](#_ENREF_69)]. The miR-143 and miR-145 expression is controlled by serum response factor (SRF) and myocardin, and these miRNAs target transcription factors including KLF4, ELK1, and angiotensin-converting enzyme[[66-68](#_ENREF_66)]. Another target of miR-145 is Oct4, Sox2 as well as Klf4, which are transcription factors for the pluripotent cell self-renewal. These miRNAs are involved in regulating cell fate decisions across different lineages[[70](#_ENREF_70)]. Loss of miR-145 induced a different SMC phenotype more similar to proliferating SMC in vascular lesions, but does not affect smooth muscle differentiation[[66](#_ENREF_66),[67](#_ENREF_67)]. Neointima formation after vessel injury was reduced in miR-145mice and to a lesser extent in miR-143mice[[68](#_ENREF_68)]. However, overexpression of miR-143 and 145 also decreased neointima formation in a rat model of acute vascular injury[[71](#_ENREF_71)]. These data suggest that miRNA-143 and miR-145 require SMC differentiation *in vitro*, but are not essential for SMC differentiation during embryonic development *in vivo*.

Another study showed that miR-10a expression increased during *in vitro* differentiation of mouse ESCs into SMCs through inhibiting histone deacetylase 4 (HDAC4) post-transcription[[72](#_ENREF_72)]. Inhibition of miR-10a impairs SMC differentiation.

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](#_ENREF_73)]. During differentiation of mouse ESC to SMCs, expression of miR-1 is steadily increased. Loss-of-function approaches using inhibitor against miR-1 results in downregulation of SMC specific markers and the decrease of the derived SMC population, that is miR-1 is required for SMC lineage differentiation in ESC derived SMC cultures. KLF, which was previously identified as miR-145 target, is a target for miR-1.

***Cardiac differentiation***

miR-1 and miR-133 were first described as critical regulators of muscle proliferation and differentiation in skeletal muscle[[74](#_ENREF_74)] and cardiac muscle[[51](#_ENREF_51)]. Both miR-1 and miR-133 promote mesoderm formation from ESCs, but these miRNAs have opposing functions during differentiation into cardiac muscle progenitors[[51](#_ENREF_51),[74-76](#_ENREF_74)].

miR-1-1 and miR-1-2 are specifically expressed in cardiac and skeletal muscle precursor cells and direct transcriptional targets including SRF, myogenic differentiation 1 and myocyte enhancement factor 2[[77](#_ENREF_77)]. Excess miR-1 in mice led to developmental arrest at embryonic during day 13.5, resulting in decreased pool of proliferating ventricular cardiomyocytes[[77](#_ENREF_77)]. Hand2, a transcription factor regulating ventricular cardiomyocyte expansion, is a direct target of miR-1[[77](#_ENREF_77)]. Contrariwise, targeted deletion of one of the two miR-1 genes (*miR-1-2*), muscle-specific miRNA, revealed numerous functions in the heart, including defective morphogenesis, electrical conduction, and dysregulated cell-cycle control in the heart[[76](#_ENREF_76)]. Consistently, drosophila miR-1 modulates cardiogenesis and maintenance of muscle-gene expression[[75](#_ENREF_75)]. Ivey *et al*[[51](#_ENREF_51)] described that miR-1 acts as a repressor of non-muscle gene and its overexpression promotes differentiation into cardiac fates by upregulating Nkx2.5, an early cardiac marker, the target of miR-1 is Notch ligand Delta-like 1. In human ESC derived embryonic bodies, miR-1 also increased myosin heavy chain (MHC) genes[[78](#_ENREF_78)]. miR-1 also increased cardiomyocyte-specific genes, and enhanced differentiation into cardiomyocytes in human-derived cardiomyocyte progenitor cells, by targeting HDAC4[[79](#_ENREF_79)]. Interestingly, transplantation of miR-1 overexpressed mouse ESCs into the border zone of infarcted mouse hearts protects against ischemia-induced apoptosis[[80](#_ENREF_80)]. In addition, miR-1 facilitates electrophysiological maturation of ESCs[[81](#_ENREF_81)]. Furthermore, when miR-1 was transfected into fibroblast, expression profiles shifts towards that of muscle[[82](#_ENREF_82)]. Recently, miR-1 induced cardiomyocyte markers, Nkx2.5, GATA-4, cTnT, and CX43, *via* downregulation of Hes-1, the downstream target molecule of Notch pathway in MSCs[[83](#_ENREF_83)].

Although *miR-1* and *miR-133* are bicistronic[[76](#_ENREF_76),[84](#_ENREF_84)], they have opposing actions. Deletion of miR-133a genes causes lethal ventricular-septal defects, and results in ectopic expression of smooth muscle genes, thus miR-133a regulates proliferation of cardiomyocyte by SRF and cyclin D2[[84](#_ENREF_84)]. Specific cardiac markers are downregulated in miR-133 overexpressed mouse and human ESCs[[51](#_ENREF_51),[85](#_ENREF_85)] and miR-133 induced proliferation of myoblasts by repression of SRF[[74](#_ENREF_74)]. But, recent study revealed that miR-133 inhibit proliferation in prostate cancer cell lines PC3 and DU145 by targeting the epidermal growth factor receptor (EGFR)[[86](#_ENREF_86)]. Concurrently, our group also found that miR-133a increased during differentiation, and its overexpression promotes cardiac differentiation in human MSCs by targeting EGFR[[87](#_ENREF_87)].

The miR-499 was enriched in adult cardiac progenitor cells and human ESCs[[78](#_ENREF_78),[79](#_ENREF_79)]. This miRNA shares many predicted targets with miR-208, which plays a crucial role in stress-adaptation of the adult heart, and is encoded by an intron of MHC[[88](#_ENREF_88)]. Overexpression of miR-499 reduced proliferation rate, and enhanced differentiation into cardiomyocytes in human cardiomyocyte progenitor cells and ESCs, through targeting Sox6, which is expressed in the heart and skeletal muscle[[79](#_ENREF_79)]. miR-499 has also been shown to play a role in the myocyte lineage and the generation of mature working cardiomyocytes, *in vitro* and after infarction *in vivo*[[89](#_ENREF_89)]. Sox6 and regulator of differentiation 1 (Rod1) is a target of miR-499. In addition to ESCs, cardiac stem cells, and cardiomyocyte progenitor cells, recently study showed that overexpression of miR-499 in rat MSCs induce cardiac differentiation through Wnt/β-catenin signaling pathway[[90](#_ENREF_90)].

miR-204 is required for human cardiomyocyte progenitor cells differentiation by targeting ATF-2[[91](#_ENREF_91)], while miR-124 inhibited cardiomyocyte differentiation of MSCs via targeting STAT3[[92](#_ENREF_92)]. Finally, deletion of miR-17-92 cluster leads to very specific defects in the development of the heart[[93](#_ENREF_93)], however, function of miR-17-92 cluster in cardiac differentiation and development is unclear.

***Neuronal differentiation***

Neural stem cells (NSCs) are giving rise to neurons, astrocyte, and oligodendrocytes, and play important roles in embryonic development and maintenance of adult central nervous system (CNS)[[94](#_ENREF_94)]. The differentiation of NSCs is tightly associated with multiple signaling pathways; the Wnt signaling regulates NSC proliferation and differentiation[[95](#_ENREF_95)], Neurog2 and Tbr2 transcription factors are linked to NSC differentiation[[96](#_ENREF_96)], an orphan nuclear receptor TLX is necessary for proliferation of adult NSCs[[97](#_ENREF_97)], and epigenetic regulators methyl CpG binding protein 2 (MeCP2), methyl-CpG binding protein 1 (MBD1), and Ezh2 are related to adult neurogenesis[[98](#_ENREF_98),[99](#_ENREF_99)]. In the mammalian brain, some miRNAs are tissue-specifically expressed, including let-7 family, miR-124, and miR-9, regulate neurogenesis[[100](#_ENREF_100),[101](#_ENREF_101)]. The brain-specific and enriched miR-124 is upregulated during CNS development and during neuronal differentiation in adult subventricular zone[[102](#_ENREF_102),[103](#_ENREF_103)]. The expression of miR-124 is induced by suppressing RE-1-silencing transcription repressor, and JAG1, Dlx2, and Sox9 are repressed by miR-124 during neurogenesis. In addition, laminin γ1 and integrin β1, are expressed in neural progenitors but inhibit neuronal differentiation, and is also targeted by miR-124, leading to neurogenesis[[104](#_ENREF_104)]. miR-9 is also highly expressed in the brain, and is involved in modulating balance between NSC self-renewal and differentiation *via* negative TLX expression[[105](#_ENREF_105)]. The overexpression of miR-9 promotes neural differentiation, whereas TLX is down-regulated. Let-7d, a family member of let-7, also targets LTX and promotes neurogenesis and reduces NSC proliferation[[106](#_ENREF_106)]. Let-7a is one of the tripartite motif-containing protein 32 (TRIM32) downstream molecules, thus, let-7a is also required for inducing differentiation of NSCs[[107](#_ENREF_107)]. Overexpression of TRIM32 induces neuronal differentiation, while inhibition of TRIM32 maintains self-renewal of neural progenitor cells. miR-137 is essential for decision of embryonic NSC fate; the overexpression of miR-137 inhibits NSC proliferation and induces accelerates differentiation by suppressing histone lysine-specific demethylase 1, a co-transcription factor of TLX[[108](#_ENREF_108)]. Additionally, in adult neurogenesis, miR-137 is controlled between proliferation and differentiation of NSC, which mediated epigenetic proteins, such as MeCP2, a DNA methyl-CpG-binding protein, Ezh2, a histone methyltransferase, and Polycomb group protein. The reduction of miR-137 expression promotes differentiation, whereas the overexpression of miR-137 increases proliferation of adult NSCs[[98](#_ENREF_98)]. Similar to miR-137, miR-184 is associated with controlling the balance between proliferation and differentiation of adult NSCs. Up-regulated miR-184 induces proliferation and reduces differentiation of adult NSCs, targeting MBD1 and Numblike (Numbl), which are related to NSC differentiation in adult brain[[99](#_ENREF_99)]. In neural stem/progenitor cells (NSPCs) isolated from adult mice, miR-106b-25 cluster (miR-106b, miR-93, and miR-25) regulates NSPCs proliferation and differentiation. miR-25 targets insulin/insulin-like growth factor-1 signaling, and 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](#_ENREF_109)]. Recently, it was found that miR-34a is involved in NSC differentiation; miR-34a promote Notch signaling by repressing Numbl, a negative regulator of Notch signaling, which inhibits neuronal differentiation[[110](#_ENREF_110)]. miR-26b activates neurogenesis by suppression of Ctdsp2 protein expression[[111](#_ENREF_111),[112](#_ENREF_112)], and miR-125b promoted differentiation and migration while inhibiting proliferation of NSPCs by targeting Nestin[[113](#_ENREF_113)] (Figure 2).

***Osteoblast, osteoclast, and chondrocyte differentiation***

The skeleton consists of both osteoblasts and osteoclasts in bones and chondrocytes in cartilages[[114](#_ENREF_114)]. Mounting evidences showed that miRNAs are an integral part of regulating bone and cartilage formation, metabolism, and homeostasis, as well as osteogenesis and chondrogensis[[115](#_ENREF_115),[116](#_ENREF_116)].

Osteoblast differentiation undergoes three stages; pre-osteoblasts (proliferation), osteoblasts/pre-osteocytes (matrix maturation), and osteocyte (mineralization) from bone marrow stromal cells[[117](#_ENREF_117)]. Each cell expresses different genes and factors; therefore, miRNAs may be selectively expressed in particular stages during osteogenesis. miR-29 has multiple distinct functions at different stages of osteoblast differentiation, and miR-29b initiates osteogenic pathway by repressing anti-osteogenic factors, HDAC4, TGF-β3, activin A receptor type IIA, beta-catenin-interacting protein 1 (CTNNBIP1), and dual-specific phosphatase. Collagen type I (COL1A1) directly targets miR-29b, and mRNA levels of COL1A1, which is down-regulated by the higher endogenous levels of miR-29b at the mineralization stage, but collagen protein accumulation is reached to a steady state[[118](#_ENREF_118)]. In addition, miR-29 suppresses osteonectin (secreted protein acidic and rich in cysteine) during the matrix maturation and mineralization phases of late differentiation[[119](#_ENREF_119)]. Although collagens and osteonectin are play an important role in bone mass and osteogenesis, inhibition of two proteins by miR-29b prevents sclerotic bone formation and increases stability of bone structure[[117](#_ENREF_117)]. Moreover, Canonical Wnt signaling is involved in osteoblast differentiation; high β-catenin is required to osteogenesis. Thus, targeting Wnt pathway by miRNAs contributes to osteogenesis[[120](#_ENREF_120)]. miR-29 family also targets Wnt signaling-mediated proteins and the expression of miR-29 is increased by Wnt activation during osteoblast differentiation. miR-29a negatively regulates Wnt receptor complex Dikkopf-related protein 1 (Dkk1), Kremen2, and secreted frizzled related protein 2 (sFRP2)[[121](#_ENREF_121)], and miR-29b down-regulates β-catenin inhibitor CTNNBIP1[[118](#_ENREF_118)]. In addition, miR-27 and miR-335 are up-regulated during osteogenesis, and targets APC gene and Dkk1, negative regulator of Wnt signaling, respectively, which leads to osteoblast differentiation[[122](#_ENREF_122),[123](#_ENREF_123)].

Only a few miRNAs contribute to osteoclast differentiation. miR-223 regulated by transcription factor PU.1, induced by M-CSF, increased miR-223 and receptor activator of nuclear factor-κB in bone marrow derived osteoclast precursors[[124](#_ENREF_124)]. Currently, miR-223 regulates NFIA, a suppressor of osteoclastogenesis, which leads to up-regulating of M-CSF receptor[[125](#_ENREF_125)]. miR-155, a key regulator in macrophages maturation from hematopoietic cells[[126](#_ENREF_126)], was studied for another osteoclastogenic miRNA. miR-155 represses MITF, a necessary transcription factor for osteoclast differentiation, inhibited osteoclastogenesis[[127](#_ENREF_127)].

Cartilages form bone via the endochondral process of ossification and the loss of miRNAs in cartilage accelerates differentiation of the mature hypertrophic chondrocytes and abnormality of bone growth[[128](#_ENREF_128)]. Cartilage-specific miR-140[[129](#_ENREF_129)] is related with palatogenesis mediating Platelet-derived growth factor D signaling in zebrafish[[130](#_ENREF_130)], and craniofacial development and endochondral bone formation *via* targeting HDAC4[[131](#_ENREF_131)] and inhibiting bitmap (BMP) signaling in mouse model[[132](#_ENREF_132)]. HDAC4 and BMP signaling contribute chondrocyte hypertrophy and osteoblast differentiation, and can be a negative effector of osteogenesis. miR-675 induces expression of cartilage-specific collagen type IIa through positive regulation of cartilage-specific Sox9, and can promote chondrogenic differentiation[[133](#_ENREF_133)]. miR-23b is also induced chondrogenic differentiation of MSCs by negatively inhibiting of protein kinase A signaling[[134](#_ENREF_134)]. Otherwise, miR-18a, miR-199a, miR-145, and miR-221 identified as negative regulators during chondrogenesis. miR-18a directly targeted the CCN family protein 2/connective tissue growth factor (CCN2/CTGF) and repressed chondrogenesis[[135](#_ENREF_135)]. miR-199a is a bone morphogenic protein 2-responsive miRNA, and significantly inhibits early chondrogenesis *via* targeting Smad1[[136](#_ENREF_136)]. In addition, miR-145 targets Sox9, a key transcription factor for chondrogenic differentiation[[137](#_ENREF_137),[138](#_ENREF_138)]. miR-221 negatively regulates Mdm2 and thereby preventing the degradation of Slug protein, which relates to inhibition of chondrogenesis (Figure 2)[[139](#_ENREF_139)].

***Others***

Despite multi-lineage differentiation potential of stem cells, little is known about the differentiation to other cell types than mentioned above. For example, the hepatic differentiation of human umbilical cord lining-derived MSCs and liver-derived progenitor cells are regulated by miR-542-5p and miR-146a[[140](#_ENREF_140)]. miR-182 is involved in differentiation of inner ear stem/progenitor cells into hair-like cells via repression of Tbx1[[141](#_ENREF_141)]. The expression of pancreatic transcription factor Ptf1a is stage-specifically different during pancreatic development; the low level of Ptf1a enhances differentiation of pancreatic progenitor cells into endocrine cells, whereas high level of Ptf1a relates to exocrine cell differentiation. The endogenous level of Ptf1a is regulated by miR-18a[[142](#_ENREF_142)]. During adipogenic differentiation of mouse ESCs, 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 are increased, and miR-17-92 cluster is down-regulated[[143](#_ENREF_143)]. Myeloid differentiation is promoted by PU 1 transcription factor, and the overexpression of miR-23a cluster in hematopoietic progenitor cells suppresses B-cell development[[144](#_ENREF_144)]. Furthermore, miRNAs is related to diploid spermatogonia differentiating into haploid spermatozoa. miR-34c is highly expressed in the late stages of spermatogenesis, which induces up-regulation of germ cell-specific genes[[145](#_ENREF_145)].

**MICRORNAS IN REPROGRAMMING**

In 2006, the astonishing research of reprogramming was published by Takahashi *et al*[[5](#_ENREF_5)], which demonstrates that somatic cells such as mouse fibroblasts, can convert pluripotent state using only four transcription factors, Oct4, Sox2, Klf4, and c-Myc. These reprogrammed fibroblasts are referred to as induced pluripotent stem cells (iPSCs), which are functionally and molecularly similar to ESCs. After one year, human iPSCs were induced in a similar manner to mouse iPSCs of the same group[[146](#_ENREF_146)]. These studies were a starting point when many researchers rushed into the somatic reprogramming strategy. Although the method of transcription factor mediated reprogramming is very simple and easy to handle, some problems, such as time , low efficiency, and the possibility of tumorigenesis, remain unsolved[[147](#_ENREF_147)]. For improving the quality of iPSCs generation, researchers focused on miRNAs, which functions are associated with regulating the epigenome. Since, etopic expression of transcription factors during reprogramming is related to epigenetic changes, miRNAs are considered as an alternative or combination factors of transcription factors[[35](#_ENREF_35)] (Figure 1).

For improving efficiency of iPSC generation, the major challenges are overcoming the reprogramming barriers. The reprogramming process undergoes two phases; the early phase (initiation phase) and the late phase[[8](#_ENREF_8)]. The early phase is a pre-pluripotent state involving an increased proliferation and change into an epithelial-like cellular state, called mesenchymal-to-epithelial transition (MET)[[148](#_ENREF_148)]. This phase is regulated by p53-induced cell-cycle repression and TGF-β-accelerated epithelial-mesenchymal transition (EMT). The late phase is conversion to iPSCs from pre-iPSCs by inducing pluripotency related genes, including Nanog, Sox2, and Lin28, and establishing the pluripotency network[[8](#_ENREF_8)]. Thus, the result of reducing the barriers is enhanced both by reprogramming efficiency and by generating functionally resembling ESCs, by miRNA-mediated epi-genetic regulation and transcriptional regulation[[8](#_ENREF_8),[148](#_ENREF_148),[149](#_ENREF_149)].

The first attempt to reprogramming is focused on highly expressed miRNAs in ESCs, which miRNAs are absent in fibroblasts and governing pluripotency. Among miR-290-295 family, miR-291-3p, miR-294, and miR-295 combination with Oct4, Sox2, and Klf4 increase the efficiency of reprogramming in mouse fibroblasts[[150](#_ENREF_150)]. In human somatic cells, miR-302a-367 and/or miR-371-373 (mouse homolog miR-290-295) with combination of Oct4, Sox2, Klf4, and c-Myc, enhances reprogramming efficiency by inhibiting TGF-β-induced EMT[[151](#_ENREF_151)]. During the early reprogramming stage, miR-17-92, miR-106b-25, and miR-106a-363 clusters, which share the seed sequences of miR-302 cluster, are shown to be highly induced[[152](#_ENREF_152)]. Overexpression of miR-106a-363 and miR-302-367 clusters promotes potent increases in iPSC generation in mouse fibroblasts with Sox2, Klf4 and Oct4 that miRNA clusters targeted TGF-β type II receptor and accelerated MET[[153](#_ENREF_153)]. In addition, the activation of BMP signaling, inducing the expression of miR-205 and miR-200 family, enhances MET[[154](#_ENREF_154)]. Thus, TGF-β and BMP signaling are important functions in promoting reprogramming by inducing MET. Further study of somatic reprogramming is a possibility of using miRNAs alone to directly promoting reprogramming. Recently, Anokye-Danso *et al*[[155](#_ENREF_155)] reported that miR-302 and miR-367 cluster successfully reprogramed mouse and human somatic cells to iPSCs without exogenous transcription factors. Interestingly, the direct transfection of mature miRNA mimics, miR-200c and miR-302-369 family in mouse and human somatic cells, promotes reprogramming. Method does not require lentiviral vectors for gene transfer[[156](#_ENREF_156)].

Contrary to the aforementioned, some miRNAs are needed to be suppressed in order to enhance reprogramming. For example, let-7 miRNAs are negative regulators of Lin28, a potent reprogramming factor. Thus, inhibition of let-7 miRNAs leads to the dedifferentiation of somatic cells to iPSCs, which induces cell proliferation genes and pluripotency genes[[40](#_ENREF_40)]. Another important miRNA barrier for reprogramming is p53-mediated pathway. p53 induces miR-34 family, suppression of the pluripotency factors Nanog and Sox2[[157](#_ENREF_157)]. The genetic deletion of miR-34a showed the efficiency and kinetics of reprogramming are increased and the pluripotency at late stage of reprogramming is established. Also, suppression of p53 by overexpressing miR-138[[158](#_ENREF_158)] or repressing miR-21 and miR-29a enhances reprogramming[[159](#_ENREF_159)]. The expression of endogenous miRNAs is regulated by transcription factors[[160](#_ENREF_160)]. miR-29b expression is directly regulated by Sox2 during iPSC generation and miR-29b is an essential mediator for Oct4, Klf2, Sox2, and c-Myc (or Oct4, Klf2, and Sox2) mediated reprogramming[[161](#_ENREF_161)].

Reported reprogramming factors, Oct4, Klf2, Sox2, and c-Myc, showed much evidences suggest that miRNAs play a crucial role in regulating stem cell fate, including reprogramming, differentiation, and self-renewal. However, some questions pertaining to the mechanism of reprogramming remain unclear. Addressing the questions will provide a profound 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 extracellular niche. Since these regulators have limitations, such as efficiency and selectivity for controlling stem cell fate, a new strategy is the use of small molecules[[162](#_ENREF_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; (3) a variety of chemical libraries provide functional optimization of small molecules[[163](#_ENREF_163)]. Recently, many small molecules that can manipulate stem cell fate, including self-renewal and lineage-specific differentiation, and somatic cell reprogramming, have been identified and characterized[[35](#_ENREF_35),[164](#_ENREF_164)].

In mouse ESCs, PD0325901 (MEK inhibitor) and CHIR99021 (GSK3 inhibitor) maintain self-renewal without feeder cells or exogenous cytokines[[165](#_ENREF_165)]. Y-27632 and thiazovivin (ROCK inhibitor) enhance the survival of human ESCs[[166-168](#_ENREF_166)], in addition, a combination of PD0325901, CHIR99021 and Y-27632 with bFGF supports maintenance of human ESCs[[169](#_ENREF_169)]. Since lineage-specific commitment of stem cells provides a possibility of therapeutic application, the studies of direct differentiation of stem cells have consistently been reported. Wnt signaling modulators promote cardiomyocyte generation in zebrafish embryos and murine ESCs[[170](#_ENREF_170)], and the inhibition of TGF-β receptor by SB431542 induces endothelial cell differentiation of human ESCs[[171](#_ENREF_171)]. Smad signaling inhibition by noggin and SB431542 directs differentiation of human ESCs into neural tissues[[172](#_ENREF_172)].

ESCs show an unlimited number of generations and a possibly differentiate into any cell types, but ethical issues still remain. Therefore, tissue-specific adult stem cells and reprogramming of somatic cells have fascinated researchers[[164](#_ENREF_164),[173](#_ENREF_173)]. Ever since Yamanaka demonstrated that Oct4, Sox2, Klf4, and c-Myc can convert mouse fibroblasts into induced pluripotent stem cells (iPSCs)[[5](#_ENREF_5)], the study of reprogramming has accelerated with epigenetic process modulators, which target histone deacetylase (HDAC)[[174](#_ENREF_174),[175](#_ENREF_175)], histone acetyltransferase[[176](#_ENREF_176),[177](#_ENREF_177)], and DNA methyltransferase[[176](#_ENREF_176),[178](#_ENREF_178)]. Recently, a chemical cocktail, HDAC inhibitors and other kinase inhibitors, enhanced the efficiency reprogramming of human fibroblasts[[175](#_ENREF_175),[179](#_ENREF_179)].

Hematopoietic stem cells are related to hematopoietic lineage, including macrophages, erythrocytes, dendritic cells, T-cells, B-cells, and NK-cells[[180](#_ENREF_180)]. HSC fate regulation by small molecules is focused on promoting self-renewal[[181-183](#_ENREF_181)]. Multipotent MSCs can differentiate into various non-hematopoietic cells by small molecules, such as chondrocytes[[134](#_ENREF_134),[184](#_ENREF_184)], osteoblasts[[185](#_ENREF_185),[186](#_ENREF_186)], hepatocytes[[187](#_ENREF_187)], cardiomyocytes[[188](#_ENREF_188),[189](#_ENREF_189)], adipocytes[[190](#_ENREF_190),[191](#_ENREF_191)], and neuronal-like cells[[192-194](#_ENREF_192)], and the maintenance of MSCs is associated with Wnt signaling[[195](#_ENREF_195),[196](#_ENREF_196)].

Although chemical approaches are a very young field in stem cell research, these small molecules show a similar biological outcome to using miRNAs for regulating stem cell fate[[35](#_ENREF_35)]. More recently, small molecules are correlated with endogenous miRNA expression and function[[197-202](#_ENREF_197)]. Therefore, the identification of relationship between miRNAs and small molecules could develop new insights into drug discovery for regenerative medicines, and powerful tools for elucidation of detailed mechanisms of miRNA expression and function in controlling of stem cell fate.

**CONCLUSION AND FUTURE DIRECTION**

More and more evidences have proved that miRNAs are a regulator for stem cell fate and are meaningful and promising. The current strategy in stem cell biology can elucidate the links between miRNAs and determine stem cell fate. Although miRNAs strictly regulates the multiple molecular signaling pathways and transcription factors in controlling stem cell fate, some significant issues have not received adequate attention. Since the current challenge heavily focused on verifying downstream targets of miRNA, the study of upstream targets of miRNAs is less known. Also, the correlation between miRNAs has not been well understood. The small molecules can not only modulate stem cell fate but also regulate the process of miRNA synthesis, the transcription factor, and/or the function of miRNAs. The challenge of identifying the relationship between miRNAs and small molecules is still at an initial stage in the biological field. Complementary to conventional and interdisciplinary strategies, including miRNAs and/or chemical manipulation for regulating stem cell self-renewal and tissue- or organ-specific differentiation and generating iPSCs, it provides a powerful tool to identify the underlying the cellular mechanisms in stem cell biology and therapeutic agents for clinical application of cell therapies and regenerative medicine.

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

**Figure 2 MicroRNAs are key regulators in stem cell differentiation.**

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

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

ESC: embryonic stem cell; HDAC: histone deacetylase; HSC: Hematopoietic stem cell; AHR: antihyaluronidase reaction; MSC: mesenchymal stem cell; PKC: Protein kinase c; PPARγ: Peroxisome proliferator activated receptorγ; PI3K: phosphatidylinositol 3-kinase.