# Chapter 2
# The Emerging Roles of microRNAs in Stem Cell Aging


**Catharine Dietrich, Manish Singh, Nishant Kumar, and Shree Ram Singh**

**Abstract** Aging is the continuous loss of tissue and organ function over time. MicroRNAs (miRNAs) are thought to play a vital role in this process. miRNAs are endogenous small noncoding RNAs that control the expression of target mRNA. They are involved in many biological processes such as developmental timing, differentiation, cell death, stem cell proliferation and differentiation, immune response, aging and cancer. Accumulating studies in recent years suggest that miRNAs play crucial roles in stem cell division and differentiation. In the present chapter, we present a brief overview of these studies and discuss their contributions toward our understanding of the importance of miRNAs in normal and aged stem cell function in various model systems.

**Keywords** microRNAs · Stem cells · Cellular senescence · Aging

## 2.1 Introduction

Aging is linked with a gradual deterioration of tissues and organs that result in various age-related diseases. Accumulative evidence in recent years suggests that miRNAs are important regulators of cellular senescence and aging [1–3]. miRNAs are small, single stranded, non-coding RNAs (22–26 nucleotides) that play a key role in gene expression post-transcriptionally [4–7]. They bind to the 3′-UTR

C. Dietrich · S. R. Singh (✉)
Stem Cell Regulation and Animal Aging Section, Basic Research Laboratory, National Cancer Institute, Frederick, MD, USA
e-mail: singhshr@mail.nih.gov

M. Singh
Mouse Cancer Genetics Program, National Cancer Institute, Frederick, MD, USA

N. Kumar
Hospitalist Division, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, USA



K. L. Mettinger et al. (eds.), *Exosomes, Stem Cells and MicroRNA*, Advances in Experimental Medicine and Biology 1056, https://doi.org/10.1007/978-3-319-74470-4_2

(untranslated region) of the target mRNAs and repress protein production by destabilizing the mRNA and silencing transcription. miRNAs' biogenesis consists of several key steps including processing by Drosha, DGCR8/Pasha, Exportin5, Dicer, RISC proteins, and P-bodies [8–12].

miRNAs work in a complex network in which each miRNA controls hundreds of distinct target genes, while the expression of a single coding gene can be regulated by multiple miRNAs. They are expressed in a tissue-specific and developmentally regulated way. The first miRNA gene, lin-4, and its target lin-14 were identified in a screening for genes that regulate developmental timing in *Caenorhabditis elegans* [9, 12]. Over several years and by employing molecular cloning and bioinformatic prediction strategies, hundreds of miRNAs have been identified in worms, *Drosophila*, mammals and plants. The human genome encodes over 1000 miRNAs and it is estimated that miRNAs target around 60% of human protein-encoding genes.

miRNAs are important mediators of embryonic development, neurogenesis, hematopoiesis, immune response, skeletal and cardiac muscle development, stress, metabolism, signal transduction, cellular differentiation, proliferation, apoptosis, stem cell fate, reprogramming, senescence and aging. Dysregulation of miRNAs pathway results in developmental defects, several human diseases, aging and cancer [13–25]. In addition, alterations in miRNAs have been shown in animal models and in humans with senescence or increasing age. This review is primarily focused on the involvement of miRNAs in the aging process of stem cells.

## 2.2 miRNAs in Stem Cell Division and Differentiation

Stem cells play a crucial role in tissue development and homeostasis. They are immature cells and have tremendous capacity for self-renewal and differentiation to form specialized cell types. Stem cells divide both symmetrically and asymmetrically. Asymmetric division of stem cells results in the formation of two daughter cells; one retains the stem cell characteristics and other one differentiates into specialized cell types (reviewed in [26, 27]).

Stem cells' self-renewal divisions are controlled by both intrinsic and extrinsic factors. Failure to maintain balance between self-renewal and differentiation of stem cells result in degenerative diseases (aging), while over-proliferation of stem cells results in tumor formation and cancer (reviewed in [27], Fig. 2.1). Accumulative studies suggest that stem cells can be used in regenerative medicine and cancer eradication (reviewed in [27]).

In recent years, miRNAs and their role in self-renewal and differentiation of stem cells in a variety of model systems have been adequately emphasized [4, 28–32]. miRNAs also function as a regulator of stem cell division. miRNAs can induce cellular differentiation by inhibiting cell cycle transition or epithelial to mesenchymal transition (EMT), and inhibiting "stemness" factors such as genetic (Sox2, Oct, and Nanog) or epigenetic (Bmi-1) [33–36].

Several miRNAs have very low level expression in stem cells, which increases upon differentiation [37]. Some miRNA can antagonize the effects of differentiation

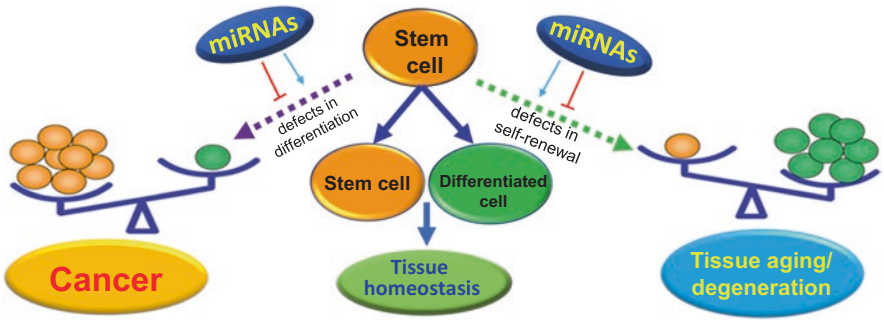


**Fig. 2.1** Schematic diagram showing how disbalance between self-renewal and differentiation of stem cells result in aging and cancer and how miRNAs regulate this process

related miRNAs [38]. There are several miRNAs that express in different stem cells, such as mammary gland progenitor cells (miR-205, [39]), skin stem cell (miR-125b, [40]; miR-203, [41]), neuronal stem cell (miR-9, [42]; miR-124, [43]; miR-184, [44]; miR-371-3, [45]; miR-6b, miR-93, and miR-25, [46]), muscle satellite stem cells (miR-1 and miR-206, [47]), hematopoietic stem cells (miR-181, miR-223 and miR-142, [48]; miR-150, [49]; miR-125a, [50]), cardiomyocyte progenitor and stem cells (miR-499, miR-1, miR-10a, miR-6086, miR-6087, miR-199b and miR-495, [51–56]), osteogenic and chondrogenic differentiation of stem cells (miR-138, [57]; miRR-23b, [58]; miR335-5p, [59]) and play an important role in balancing their self-renewal and differentiation process.

## 2.3 miRNAs in Stem Cell Aging

Stem cells play an important role in replacing aged or damaged cells in the tissues and organs of organisms. As we age, the regenerative capacity of stem cells progressively declines, which results in tissue or organ dysfunction. In recent years, several miRNAs have been identified to play crucial role in defining the regenerative capacity of stem cells during aging (reviewed in [17, 18]). miRNAs that regulate the stem cell self-renewal and differentiation process are therefore important in the aging process (Fig. 2.1).

In the following section, we will explore these miRNAs in age associated changes to stem cell function in various model systems, including human.

### *2.3.1 C. elegans*

*C. elegans* has been used as a powerful model system for investigating stem cell self-renewal, maintenance of pluripotency and reprogramming of differentiation [60, 61]. The first miRNA *lin-4*, and its target *lin-14* were identified in *C. elegans*

[9, 12]. Several miRNAs have been identified that regulate stem cell maintenance, proliferation and aging of germline and seam cells in *C. elegans* ([62–68], Table 2.1) as well. In *C. elegans*, life-span is regulated by signaling between the germline and the soma. miRNAs such as *lin-4* and its target *lin-14* has been shown to regulate aging in *C. elegans*. It has been demonstrated that mutation in *lin-4* resulted in a shortening of lifespan; on the other hand, mutation in its target gene, *lin-14* resulted in lifespan extension, which is mediated by its effector- DAF-16 [94]. Shen et al. [67] have demonstrated that removing germline stem cells (GSCs) from *miR-84;miR-241* gonads resulted in shortening of lifespan and upregulation of DAF-12 signaling. Further, they found that DAF-12 target miRNAs such as *miR-84; miR-241* are required for gonadal longevity through DAF-16 [67]. A study by Boulias et al. [62] shown that *miR-71* acts in neurons and is responsible for lifespan extension in GSC mutants by regulating DAF-16/FOXO. Recently, Wang et al. [68] reported that knockdown of *lin-28* extends lifespans and promotes the meiotic entry of GSCs. They further showed that *lin-28* is required for proper establishment of the GSC pool and acts in the germline to regulate GSC number because the mutant of *lin-28* shows smaller pool of GSC in young adult worms [68]. In addition, they reported that lin-28 exerts its effects on GSC number and lifespan though *let-7* and AKT-1/2 and requires DAF-16 to influence GSC number and longevity [68]. In addition to germline system, other studies have shown that some miRNAs regulate neuronal regeneration and seam stem cell function in older worms [63, 95]. Zou et al. [95] also reported that in older anterior ventral microtubule (AVM) axons, *let-7* inhibits their regeneration by downregulating *lin-41*. In the seam stem cells, miRNAs such as let-7 and lin-4 promote differentiation by inhibiting their self-renewal [63].

### *2.3.2 Drosophila*

*Drosophila* have proven to be a best genetic model system for investigating aging related changes in stem cell function [69, 96, 97]. Several miRNAs have been identified that regulate self-renewal and differentiation and aging of germline and somatic stem cells in *Drosophila*. Recent studies demonstrated that miRNA pathways play an important role in the GSCs of *Drosophila* gonads [28, 69, 98–106]. Hatfield et al. [99] demonstrated that loss of function of *dicer*-1 results degeneration of developing egg chambers due to deficiency in germline cyst production. Toledano et al. [69] have shown that let-7 controls aging of *Drosophila* testis GSC and mediates age dependent decrease in the IGF-II messenger RNA binding protein (Imp), which in turn results in age-dependent decline of GSCs ([69], Table 2.1). Chen et al. [51] have reported that *lin-28* is required for adult intestinal stem cells (ISCs) expansion. They found persistent reduction of total numbers of ISCs in *lin-28* mutants with age. In miR-275 mutants, it has been shown that with age the proportion of ISC increases at the expense of more mature differentiated cells, which results in gut dysplasia and shorten life span ([70, 107], Table 2.1).

**Table 2.1** miRNAs involved in stem cell aging and senescence

| Stem cell type | miRNAs | Roles in | References |
|---|---|---|---|
| *C. elegans* GSCs | miR-84, miR-241, miR-71, LIN-28, let-7 | Aging | [62, 67, 68] |
| *Drosophila* testis GSC | let-7 | Aging | [69] |
| *Drosophila* ISC | Lin-28, miR-275-305 | Aging | [51, 70] |
| Mouse NSC | let-7b | Aging | [20] |
| Human BM-MSC | let-7f, miR-29c, miR-369-5p, miR-371, miR-499 | Senescence | [71] |
| Human BM-MSC | miR-17, miR-19a, miR-19b, miR-20a, miR-519d | Aging | [72] |
| Mouse/human BM-MSC | miR-543, miR-590-3p | Aging | [73] |
| Human BM-MSC | miR-335 | Senescence/ aging | [74] |
| Human BM-MSC | miR-29c-3p | Senescence | [75] |
| Human BM-MSC | miR-199b-5p | Aging | [76] |
| Mouse BM-MSC | miR-183-5p | Senescence | [14] |
| Mouse BM-MSC | miR-17 | Aging | [77] |
| Human BM-MSC | miR-140, miR-146a/b, miR-195 | Senescence | [78] |
| Rhesus monkey BM-MSC | let-7f, miR-23a, miR-125b, miR-199-3p, miR-222, miR-558, miR-766 | Aging | [79] |
| Human UC-MSC | let-7a1, let-7d, let-7f1, miR-23a, miR-26a, miR-30a | Senescence | [80] |
| Human UC-MSC | miR-200c, miR-214 | Senescence | [81] |
| Human UC-MSC | miR-141-3p | Aging | [25] |
| Mouse BM-HSC | miR-146a | Aging | [82] |
| Mouse BM-HSC | miR-125b | Aging | [24] |
| Mouse BM-HSC | miR-132, miR-212 | Aging | [83] |
| Human ASC and BM-MSC | miR-122, miR-510, miR-452, miR-335, miR-935, miR-142-3p, miR-483-3p, miR-203, miR-153, miR-1277, miR-141 | Aging | [84] |
| Human ASC | miR-27b, miR-106a, miR-199a, let-7 | Aging | [85] |
| Rat ASC | miR-143, miR-204 | Aging | [15] |
| Human ADSC | miR-17hg, miR-100hg | Senescence | [86] |
| Human SC (satellite) | let-7b, let-7e | Aging | [87] |
| Mouse and human satellite and myoblast cells | miR-143-3p | Aging | [88] |
| Porcine muscle stem cell | miR-1, miR-206, miR-24 | Aging | [89] |
| Tendon stem/ progenitor cell | miR-135a, miR-140-5p | Senescence | [90, 91] |
| Mouse cardiac progenitor cells | miR-675 | Senescence | [92] |
| Human DPSC | miR-152 | Senescence | [93] |

### *2.3.3 Mammalian System*

Several studies reported the important roles of miRNAs in self-renewal, pluripotency, proliferation, differentiation, senescence and aging of stem cells in various tissues and organs. We will be discussing studies involving miRNAs and aging on different stem cell system in the following subsections (Table 2.1).

#### 2.3.3.1 Neural Stem Cells

Nishino et al. [20] have shown that loss of self-renewal potential in old neural stem cells is associated with age-dependent upregulation of let-7b that ultimately downregulates the expression of HMGA2, a repressor of the INK4a/ARF locus, which results in up-regulation of p16 and p19, which then results in the decline proliferation and self-renewal of neural stem cells (NSCs) [20].

#### 2.3.3.2 Mesenchymal Stem Cells

Mesenchymal stem cells (MSC) are multipotent stem cells that can differentiate to form various specialized cell types. MSCs are isolated from several tissues including bone marrow (BM), umbilical cord blood (UCB), adipose tissues and muscle tissues. The regenerative capacity of MSCs provide great potential for regenerative medicine. Understanding the culture and differentiation of MSCs during the aging and senescence process has vital implications in clinics [18, 108]. Several miRNAs identified regulate age-associated alterations in MSCs [14, 15, 71–73, 75, 85, 86]. Wagner et al. [71] have addressed the impact of replicative senescence on human MSC cultures. They found upregulation of miR-371, miR-369-5p, miR-29c, miR-499 and let-7f is because of the passage effect, not because of replicative senescence. Upregulation of these miRNAs reduces the proliferative potential of MSCs, which results in loss of adipogenic differentiation potential [71]. Hackl et al. [72] have selected four replicative cell aging models (endothelial cells, renal proximal tubule epithelial cells, skin fibroblast cells, and $CD8^+$ T cells) and three organismal aging models (foreskin, MSCs, and $CD8^+$T cells form young and old donors). Hackl et al. [72] found that miR-17 was downregulated in all seven models, whereas miR-19b and miR-20a were downregulated in six models, and miR-106a was downregulated in five models. These results of this study identify miRNAs as novel markers of cell aging in humans [72].

To understand the cellular aging of human MSCs, Lee et al. [73] shown that AIMP3 (aminoacyl-tRNA synthetase-interacting multifunctional protein-3)/p18 regulates cellular aging in MSCs through miR-543 and miR-590-3p. Tomé et al. [74] have demonstrated that both aging and continuous propagation of MSCs induce a gradual increase in miR-335 expression, which is in turn associated with cell senescence alterations and results in loss of their therapeutic capacity, this is mediated by inhibition of activator protein 1 (AP-1) activity. Further, miR-29c-3p has

been identified to promotes the senescence of MSCs by targeting CNOT6 through p53-p21 and p16-pRB pathways [75]. They further found that both the p53-p21 and p16-pRB pathways were enhanced during the miR-29c-3p-induced senescence of MSCs. Peffers et al. [76] found the age-related increase of miR-199b-5p expression in MSCs, which results in age-related deterioration of MSC function through regulating SIRT1, TGFα and PODXL. Recently, Davis et al. [14] reported that aging and oxidative stress can dramatically increase the miR-183-5p cargo of extracellular vesicles in the bone marrow, which results in reduction in cell proliferation, osteogenic differentiation and the increased senescence of BM-MSCs mediated by reduction of heme oxygenase-1 (Hmox1) activity.

The senescence-associated secretory phenotype (SASP) has been found to be a novel mechanism that associates cellular senescence to tissue dysfunction. There is limited information are available to show the age-dependent alterations in the secretory behavior of stem cells. Hisamatsu et al. [77] identified growth differentiation factor 6 (Gdf6) as a regenerative factor secreted from young MSC, their expression was controlled by the miR-17, whose expression was downregulated with age. In addition, they found that miR-17 overexpression restores the differentiation potential of old MSCs, and the upregulation of Gdf6 ameliorates geriatric pathologies. Okada et al. [78] investigated the role of miRNAs in stem cell aging and their roles in cardiac repair. They reported that miR-195 upregulated in old MSCs induces stem cell senescence, resulting in a declining of their regenerative potential by deactivating telomerase reverse transcriptase (tert), and how downregulation of miR-195 can restore MSC aging, which suggests that rejuvenation of old MSCs by miR-195 inhibition could be used as a potential autologous strategy for cardiac repair in older patients [78]. Yu et al. [79] investigated the effect of aging on the properties of Rhesus Monkey bone marrow-MSC (rBMSC) and found decrease in proliferation and differentiation capacity of MSC with age. Their miRNA expression profiles identified an upregulation of miR-766 and miR-558 and downregulation of miR-let-7f, miR-125b, miR-222, miR-199-3p, miR-23a, and miR-221 in old MSCs compare to young MSCs.

In context of cellular senescence, which involves a decline in stem cell self-renewal and epigenetic regulation of gene expression, Lee et al. [80] demonstrated that the cellular senescence of human umbilical cord-derived MSCs (UCB-MSCs) caused by a decrease in histone deacetylases (HDACs) result in downregulation of high mobility group A2 (HMGA2) and increased expression of p16, p21 and p27. Further, they found that miR-23a, miR-26a and miR-30a inhibit HMGA2 to elevate cellular senescence in UCB-MSCs [80]. So et al. [81] further shown that DNMTs regulate cellular senescence of UCB-MSC by controlling the expression of p16 and p21. In addition, they found that the expression of miR-220c and miR-214 were upregulated in senescent UCB-MSCs. It has been reported that prelamin A accumulated in MSCs during cellular senescence, however the molecular mechanisms responsible for prelamin A accumulation in hMSCs was not known. Yu et al. [25] reported that ZMPSTE24, which is associated in the post-translational maturation of lamin A, is mainly responsible for the prelamin A accumulation, which results in cellular senescence in hMSCs. Their results provide a novel mechanism regulating

MSC aging, which has broad therapeutic implication in reducing age-associated MSC pool exhaustion [25].

#### 2.3.3.3 Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) have enormous self-renewing and differentiation capacity; they can form all types of blood cells including immune cells. Several miRNAs are reported to regulate HSC numbers during stress, aging and contribute to age-related disorders such as acute myeloid leukemia (AML). In this context, Zhao et al. [82] reported that miR-146a regulates HSC numbers during chronic inflammatory stress such as miR-146a-deficiency. This deficiency results in progressive decline in the quality of long-term HSCs from young mice compared to wild type mice. This study has identified miR-146a to be a crucial regulator of HSC in mice during chronic inflammation [82]. Yalcin et al. [24] characterized the expression profiles of HSCs from young and old mice and mice treated with anti-aging interventions (such as calorie restriction and rapamycin) and found miR-125b as a critical regulator of HSC aging and that anti-aging interventions can employ their positive effects on HSC potential by regulating miR-125b expression [24]. Further, Mehta et al. [83] found that the miRNAs' 212/132 cluster is elevated in HSCs and upregulated during aging. This cluster also regulates HSCs self-renewal and survival during aging by targeting the transcription factor FOXO3. To understand the effect of biologic age-induced miRNA changes on MSCs, Pandey et al. [84] investigated miRNA profiles of MSCs derived from adipose tissue (ASCs) and bone marrow (BMSCs) from young and old human donors using an unbiased genome-wide approach. Their analysis showed significant differences in 45 miRNAs in BMSCs and 14 in ASCs. In addition, many miRNAs were downregulated in both ASCs and BMSCs in specimens from older donors as compared to younger donors. Their finding on miRNA profiling suggest that miRNAs play an important role MSC aging and ability to block inflammation and enhance cellular repair [84].

#### 2.3.3.4 Muscle Stem Cells

Aging causes loss of skeletal muscle (sarcopenia), which results in falls and fractures. miRNAs are potential regulators of skeletal muscle mass and function. Studies in rodents and humans have also shown that aging reduces the satellite stem cell pool and their ability to proliferate and differentiate in humans [109, 110]. Drummond et al. [87] performed miRNA analysis on skeletal muscle biopsies of 36 young and older adults, using a miRNA array and confirmed that the expression of Let-7b and Let-7e was dramatically increased in older compared to younger subjects. In addition, they demonstrated that increased Let-7 expression is linked with a low number of satellite cells in older humans, where they found lower expression of PAX7 mRNA. These results suggest that low number of satellite cells can affect renewal and regeneration of muscle cells [87]. Redshaw et al. [89] measured the expression

of miR-1, miR-24 and miR-206 in the muscle stem cells that were isolated from two muscles: the diaphragm (DIA) and the semimembranosus (SM), from young and old pigs. They found that all three miRNAs are enriched in skeletal muscles. In addition, they showed older animals show low expression of miR-1 and miR-206, except for whereas, miR-24, which show higher expression [89]. Using satellite cells and primary myoblasts from mice and humans and an in vitro regeneration model, Soriano-Arroquia et al. [88] have shown that disrupted expression of miR-143-3p and its target gene, Igfbp5, plays crucial part in muscle regeneration in vitro because their expression is disrupted in satellite cells from older mice. In addition, they found miR-143 as a regulator of the insulin growth factor-binding protein 5 (Igfbp5) in primary myoblasts. Their findings suggest that dysregulation of miR-143-3p:Igfbp5 interactions in satellite cells with age could diminish the satellite cells' function [88]. Lee et al. [111] analyzed the miRNA expression profiles of myoblasts isolated from young and old mouse skeletal muscles and identified miR-431 as a novel age-associated miRNA which regulates SMAD4 expression and promotes differentiation and regeneration of old skeletal muscle. The low reprogramming efficiency in cells of older patients is a major challenge, in this context, Kondo et al. [112] demonstrated that blocking miR-195 expression could be helpful in reprogramming efficiency in old skeletal myoblasts.

#### 2.3.3.5 Cardiac Progenitor Cells

Aging is the primary risk factor for cardiovascular diseases. It affects cardia progenitor/stem cells and suppresses their regenerative ability. miRNAs have emerged as important regulators of cardiovascular function and there are few miRNAs play crucial roles in cardiac aging [113, 114]. C-kit(+) cardiac progenitor cells (CPCs) have appeared as a good tool for the treatment of heart diseases [115]. However, the senescence of CPCs decrease their regenerative potential. Cai et al. [92] shown that melatonin antagonized premature senescence of CPCs via the H19/miR-675/USP10 pathway, which gives a novel mechanism by which melatonin inhibits CPCs senescence by promoting miR-675. Endothelial progenitor cells (EPCs) are known to contribute to the regeneration of endothelium. However, aging results in EPCs senescence, which leads to increased cardiac risk, reduced angiogenic capacity, and loss of cardiac repair function. Zhu et al. [116] provide the mechanism by which this EPCs senescence in aged mice. They found that miR-10A* and miR-21 control EPC senescence via suppression of Hmga2 expression, which suggests that modulating these two miRNAs could be a novel therapeutic intervention in ameliorating EPC-mediated angiogenesis and vascular repair.

#### 2.3.3.6 Tendon Stem/Progenitor Cells

Aging of tendon stem/progenitor cells (TSPCs) may result in tissue degeneration and subsequent injury. Several studies have demonstrated that aging can affect the proliferation and differentiation capacity of TSPCs [117, 118], but the molecular

mechanism that regulates this process is still not clear. Recently, Chen et al. [90] investigated whether miRNAs modulate senescence of TSPCs. They found that miR-135a regulates senescence of TSPCs by targeting Rho-associated coiled-coil protein kinase 1 (ROCK1). miR-135a was dramatically downregulated in aged compared with young TSPCs. In addition, they reported that overexpression of miR-135a in young TSPCs inhibits senescence and restores their proliferation and differentiation capacity, while loss of miR-135a in aged TSPCs results in senescence of TSPCs. These studies suggest that miR-135a regulates TSPC senescence by repressing ROCK1 [90]. PIN1, a peptidyl-prolyl cis/trans isomerase, has been shown in age-related bone homeostasis and adipogenesis. Chen et al. [91] investigated the role of Pin1 in the aging of human TSPCs. They found a dramatic decrease in Pin1 expression during prolonged in vitro cultures of human TSPCs. Their loss-of-function and gain-of-function, studies show that overexpression of Pin1 delayed the progression of cellular senescence, while downregulation of Pin1 promoted senescence in TSPCs. In addition, they demonstrated that miR-140-5p regulates Pin1 expression at the translational level, which suggests miR-140-5p affects TSPC aging by targeting Pin1 [91].

#### 2.3.3.7 Dental Pulp Stem Cells

Dental pulp stem cells (DPSCs) have emerged as a viable cell source for regenerative medicine in recent years [93, 119, 120]. Several miRNAs are known to control human DPSCs proliferation and differentiation [121, 122]. Recently, Gu et al. [93] studied the human DPSCs senescence and have shown that miR-152 is upregulated during HDPSC senescence. Further, they found that Sirtuin 7 (SIRT7), a target of miR-152, is downregulated in senescent HDPSCs; blocking miR-152 enhanced SIRT7, and blocking HDPSC senescence. In addition, overexpression of SIRT7 restored miR-152-induced senescence. Their results suggest that the miR-152/SIRT7 axis are crucial in the regulation of HDPSC senescence [93].

## 2.4 Conclusion

miRNAs are the novel regulatory molecules in various biological processes. The discovery of miRNAs has opened a new avenue in aging research, which will help researchers to obtain an extensive understanding of the molecular mechanism underlying this complex process. Altered expression of miRNAs resulted in developmental defects, loss of tissue homeostasis, cellular senescence, aging and cancer in various model organisms including humans. miRNAs play important roles in the stem cell self-renewal and differentiation processes, and regulate stem cell aging through multiple targets. Thus, miRNAs provide novel therapeutic options for the senescence and aging of stem cells in humans.

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