



MINI-REVIEW

MicroRNAs: Small Regulators of Tissue Regeneration

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ABSTRACT

MicroRNAs (miRNAs) are small molecules that are involved in the regulation of cellular events. They can monitor protein production using a kind of gene expression inhibition called post transcriptional gene regulation. Nowadays a lot of them have been found in different kind of cellular process so they have a wide range of functions from common cell tasks to roles in the regulation of special functions including regeneration of damaged tissues. In recent years, there has been an increasing interest in the field of miRNAs. This paper will review the research conducted on the roles of miRNAs in stem cells and tissue/organ regeneration.

Keywords: Stem cells, Self-renewal, Differentiation, Paracrine effects, MiRNA, Regenerative medicine, Molecular mechanisms.

MiRNAs are defined as a small non coding RNA molecules about 22 nucleotides in length (1). Regularly cell use these molecules to control translation of mRNA to related protein called post-transcriptional regulation of gene expression. MiRNAs are not specific for animal kingdom because they reported in plants and also some viruses (2, 3). MiRNAs can attach to their target mRNAs using complementary hydrogen bonds between nucleotides. After bonding RNA induced silencing complex (RISC) is triggered, the cleavage and degradation of mRNA being started so protein production will be inhibited (4). In another strategy pairing of miRNA and mRNA lead to less translation of mRNA by ribosomes.

As a result, both methods reduce the amount of protein production in the cell. First miRNA discovery has been reported in 1990s (5). During this 25 years so many member of this family have been discovered. Today it is good understood that they have important roles in different cellular process and clinical importance including cancer (6), as a diagnosis tools or biomarkers (7) or even neurogenesis (8), and stem cells function such as differentiation, self-renewal and paracrine effects (9) and subsequently tissue regeneration (10). MiRNA fine tuning and regulation and its role in cell fate demonstrated in Figure 1.

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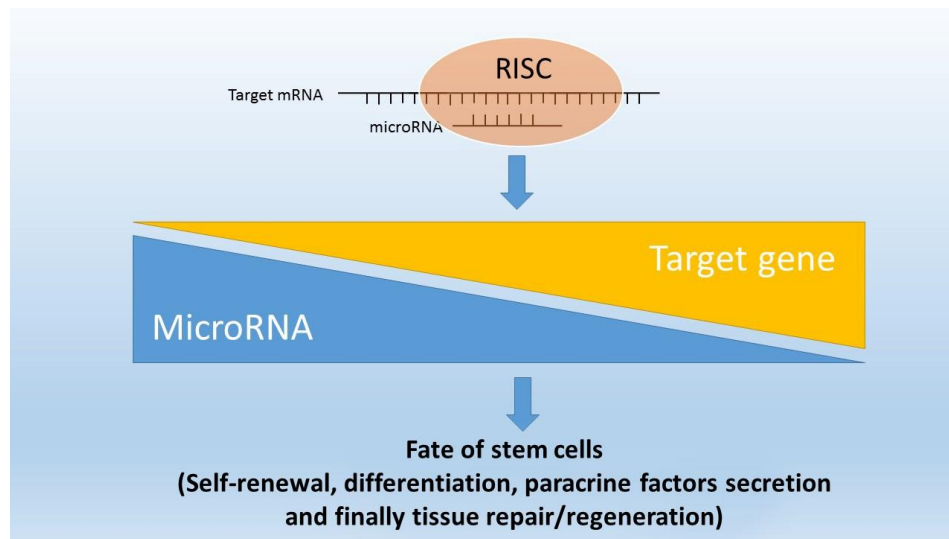


Figure 1. Function of miRNAs. When a miRNA makes complementary pairing with its mRNA target, RISC started to negatively regulate mRNA using degradation or translation inhibition. So, more amounts of miRNA results in more reducing of the mRNA target expression and finally cell or tissue could be directed to special fate.

Regeneration

Since diseases and injuries can damage normal morphology and physiology of a tissue and organ, so there is an increasing number of researches on regeneration studies because of its importance to human life (12, 20). Recent studies have shown that in every regeneration pathway some miRNAs play critical role in controlling gene expression (11, 20-22), for example, MiR-351 plays as a regulator for progenitor cell proliferation and survival during muscle regeneration (21). The roles of some miRNAs have been shown in Table 1. Therefore, by better understanding the roles of these molecules we can make better decisions on their clinical use from promoting differentiation of different kinds of stem cells *in vitro* or inducing whole tissue/organ regeneration *in vivo*.

MiRNA-mediated molecular mechanisms to induce different organ regeneration

Throughout the past decade, stem cells discoveries have led to the development of many approaches for the treatment of degenerative diseases and also cancer (23). Stem cells and tumor cells have several important similarities. For example, both can proliferate extensively (24, 25).

Table1. miRNAs roles in regenerative medicine. miRNAs are involved in some important regeneration events.

MicroRNA	Regulated gene	function	Species	Ref
miR-382	PTEN	Liver regeneration	mouse	(11)
miR-206, miR-1 and miR-133a/b	Pax7	Regeneration of skeletal muscle	mouse	(12)
miR-34a	betaB (INHBB) and Met	Liver regeneration	mouse	(13)
miR-125b	Sema4D	Spinal cord regeneration	rat	(14)
miR-29b and miR-223	eva1a	Nerve regeneration	zebrafish	(15)
miR-21	igfbp3 and fosl1	Kidney regeneration	zebrafish	(16)
miR-206	TIMP-3	Cardiac regeneration	mouse	(17)
miR-203	Pax6b	Retina regeneration	zebrafish	(18)
miR-135	Hoxa2	Bone regeneration	rat	(19)

Like other cells, stem cells have specific epigenetic mechanisms for the maintenance of their specific properties. Therefore, understanding how miRNAs impact the epigenetic maintenance of pluripotency or induction of differentiation is very important in the field of stem cell technology (26, 27).

For several years, siRNAs have been utilized to study the properties of stem cells (28). Discovering miRNAs in stem cells has also provided a new insight into the molecular means of pluripotency and tissue/organ regeneration. However, these studies are still in their infancy. In order to recognize the miRNA-mediated molecular mechanisms in stem cells and to help the application of these cells in regenerative medicine, several questions must be addressed: What is stem cell-specific miRNAs set? Under what conditions they will be expressed? What are their target mRNA molecules? How they guide the self-renewal and differentiation pathway? (29-31).

The expression profile of miRNAs, which was cloned from human embryonic stem cell (hES) cells, can be categorized into 4 groups: (1) miRNAs that are expressed in ES cells as well as in embryonic carcinoma (EC) cells, these miRNAs might have conserved functions in mammalian stem cells. (2) MiRNAs that are expressed exclusively in ES cells but not in other cells, including EC cells, these miRNAs may have specific functions in ES cells. It would be interesting to dissect the molecular foundation for the existing differences among 2 pluripotent stem cells; ES and EC cells. (3) MiRNAs that are infrequent in ES cells, but abundant in HeLa and STO cells, these stage-specific miRNAs may have roles in the regulation of development and differentiation, for instance, *let-7* in *C. elegans*. (4) These are expressed in most tested cell lines, these miRNAs may contribute to several essential cellular functions (32). Some miRNAs of these groups listed in Table-2. Loss of all miRNA functions in mice resulted in embryonic mortality with a loss of stem cell population in the epiblast stage and failure to form a primitive streak (33). These data suggested that miRNAs play a major role in embryonic development.

Table2. Cell type related expression of miRNAs.

Cell type related expression	MicroRNA
In ES cells as well as in EC cells	miR-302b, miR-302b, miR-302c, miR-302c, miR-302a, miR-302a, miR-302d, and miR-367
In ES cells but not in other cells, including EC cells	miR-200c, miR-368, miR-154, miR-371, miR-372, miR-373, and miR-373
ES cells, but abundant in HeLa and STO cells	<i>let-7a</i> , miR-301, miR-374, miR-21, miR-29b, and miR-29
In most tested cell lines	The last category consists of miR-16, miR-17-5p, miR-26a, miR-92, miR-103, miR-130a, and miR-222.

Since vital regulation of protein expression is important for controlling the balance between self-renewal and differentiation in stem cells, the number of studies on miRNAs within this model is rapidly increasing. For example, Poitz et al. showed monocyte-to-macrophage differentiation mediated by a miRNA-dependent mechanism using miR-17 and miR-20a (34). Data indicated that stem cells have individually separate and distinct miRNA expression profiles, which may account for the inherent stem cell features of self-renewal and pluripotency (9, 35, 36). In particular, miRNAs have been implicated in down regulation of cell cycle checkpoint proteins during germ stem cell division (37, 38). Researches revealed that modifications in miRNA expression can trigger or hinder stem or progenitor cell differentiation within different cell lineages, such as hematopoietic cells (39), cardiomyocytes (40), myoblasts (41), and neural cells (42).

Small populations of cancer cells with stem cell properties have been identified in recent years. These cells have been called cancer stem cells (CSCs) and have proposed a possible source of relapse in cancer patients (43, 44). MiRNAs have also been strongly implicated in regulating the functions of cancer stem cells (45). Hence, understanding the biological grounds of stem cells and cancer stem cells is necessary in the field of regenerative medicine and cancer therapy.

Guimaraes-Sternberg et al. reported that a synthetic 23-mer 2-oxymethylated oligonucleotide resembling the miR-181a sequence, blocked the calcium-induced differentiation, and at the same time

increased cellular pre-miR-181a intensity and induced DNA fragmentation and cell fatality. The stress-induced modulation of hematopoietic miR-181a levels through AChE, PKC and PKA cascade(s) implies miRNA mimics can be used to change the fate of hematopoietic tumour cells towards apoptosis and/or differentiation (46). Expression of miR-181 which has been preferentially performed in the B-lymphoid cells of mouse bone marrow and hematopoietic stem/progenitor cells resulted in an increased portion of B-lymphoid derived-lineage cells by differentiation assays in adult mice. According to these results, miRNAs are building blocks of a molecular circuitry that controls mouse hematopoiesis, indicating that miRNAs have similar regulatory functions for other parameters in vertebrate development (47). From all these studies, it can be implied that studying miRNAs is very important because of their roles in stem cell pluripotency and differentiation and fate (48-50).

Role of miRNAs in paracrine effects of stem cells

In recent years, new studies have been done to make clear the connection between the paracrine signaling and miRNAs. Now, miR-21 has been found in the pericardial fluid of C57BL/6N mice and associated with regenerative paracrine signal of cardiomyocyte hypertrophy (51). MiR-145 uses paracrine mechanism to promote patterning of both gut layers in embryonic stages (52).

Conclusion

A strong relationship between miRNAs and the amount of their target has been reported in the literature. Understanding gene regulation and mRNA fine tuning is very important for better cell selection especially for regeneration and therapeutic purpose of cell therapy. Among regulatory molecules, miRNAs are key molecules because they can change cell fate and functions.

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