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Mini Review

A novel role of miR-302/367 in reprogramming

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ABSTRACT

Ever since the technique of coaxing ordinary skin cells into becoming pluripotent stem cells (iPSCs) has been developed, which have the potential to become any cell or tissue in the body, efforts were made to improve the approach because some major challenges. Increasing evidence suggests that several microRNAs (miRNAs) are involved in early embryonic development and embryonic stem cell formation, known as embryonic stem cell (ESC)-specific miRNAs, particularly the miR-302 family. We summarized here a novel approach to generate iPSCs by using miR-302 and its related miRNAs such as miR-367. The development of this miR-302/367-mediated iPSC (termed mirPSC) may provide tools to deal with the obstacles facing some current iPSC reprogramming methods. The mechanism by which miR-302/367 induce iPSC reprogramming is proposed.

1. Introduction

MicroRNAs (miRNAs), a class of small, widely-distributed 19–25 nt non-coding RNAs, plays an important posttranscriptional regulatory role by targeting mRNA for cleavage or translational repression based on sequence complementarity between the miRNA and its targeted mRNAs [1–3]. The processing of miRNAs involves RNA polymerase II, Drosha/DGCR8, Ran-GTP/Exportin-5, Dicer/Ago2, and RNA-induced silencing complex (RISC), which delivers mature miRNAs to their targets (Fig. 1). The seed sequence of the miRNA (7–8 nt at the 5′ end) recognizes a specific sequence motif within the 3′ untranslated region of the mRNA target based on imperfectly or partially matched binding to silence the mRNA expression so that one miRNA often targets several to hundreds of mRNAs [1,3]. In addition, two or more different miRNAs may target the same single mRNA. Therefore, the possibility for fine orchestration of translation of mRNAs by miRNAs is enormous. Numerous miRNAs are involved in inflammation, metabolism, diabetics, cancers, cell senescence, cell differentiation, and, embryonic development, suggesting an important miRNA-mediated gene regulatory system and fine-tuning cellular and developmental events through the mechanism of RNAi-like gene silencing [4–7].

Induced pluripotent stem cells (iPSCs) are genetically reprogrammed cells by introducing transcriptional and/or other factors such as Oct3/4, Sox2, Nanog, and c-Myc [8], and Klf4 or Oct3/4, Sox2, Nanog, and LIN-28 [9], resulting in cells maintaining characteristics of embryonic stem cells. This process of reprogramming offers exciting promise for future therapies, but significant technical hurdles remain to be overcome such as efficiency and tumor formation. Recent studies also established that introduction of miRNAs into cells represents a simpler method of reprogramming, particularly miR-302 and its related miR-367, which increase the efficiency and may be tumor-free [7,10,11]. We briefly reviewed the current knowledge of miR-302/367-mediated induction of cancer and somatic cells to become embryonic pluripotent stem cells.

2. miR-302 in embryonic stem cells

The transition from oocytes to zygotes depends on a large volume of maternal RNAs in the oocyte cytoplasm, which are degraded rapidly as early as 2–4 cell stages [12,13]. These findings suggest that maternal RNAs contain inhibitors of the zygotic gene transcripts (mRNAs) to prevent pre-mature embryogenesis and to maintain pluripotent stem cell self-renewal. Mouse oocytes lacking Dicer arrest in meiosis I stage [14], suggesting that miRNAs in ooctyes may play an important role in maintaining pluripotent stem cells. Embryonic stem cell (ESC)-specific miR-302 is highly expressed at early stages of development and then declined prior to differentiation [15–17]. Several embryonic cell and germ cell lines also expressed high levels of the miR-302 cluster, including human tetracarcinoma NTeraD1, mouse embryonic carcinoma P19, and mouse testicular malignant germ cell tumors [18–20]. In human ESCs and iPSCs, miR-302 is the most predominant miRNA species [7,17,21–27]. The level of miR-302 cluster,

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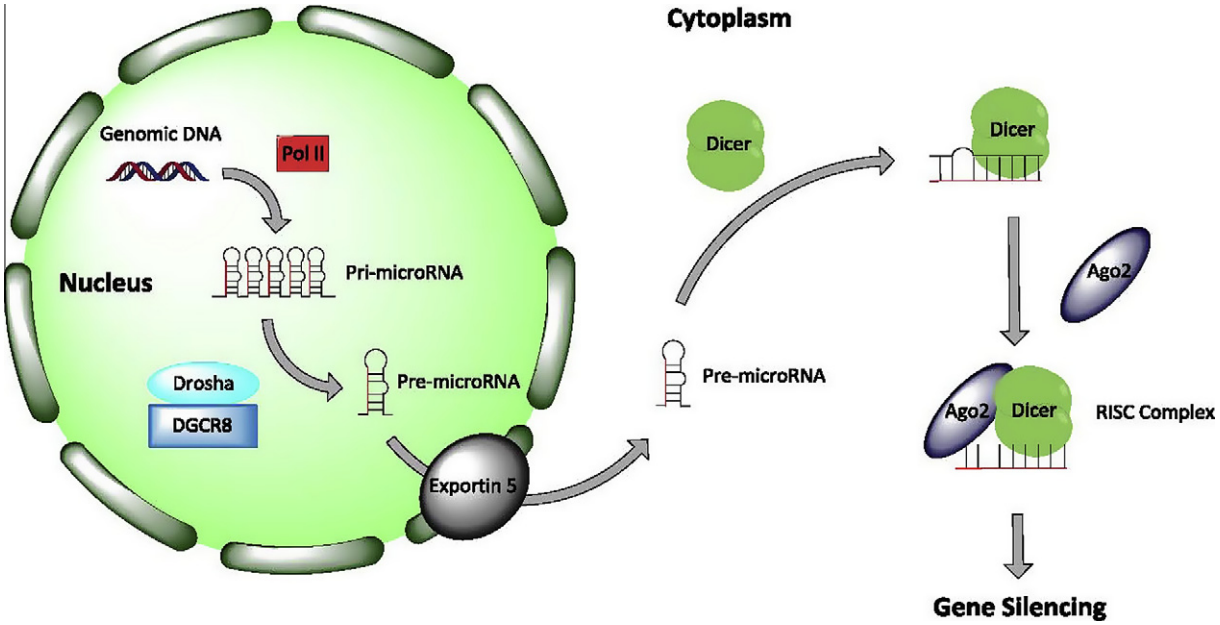

Fig. 1. Biogenesis of miRNAs and the assembly of RNA induced silencing (RISC) complex. miRNA genes are transcribed by RNA-polymerase II (Pol II) and form pri-miRNAs (long transcripts termed primary RNAs), which are processed by Drosha and the microprocessor complex subunit DiGeorge syndrome critical region gene 8 (DGCR8), resulting in pre-miRNAs. The pre-miRNAs are transported from the nucleus to the cytoplasm by Exportin 5. In the cytoplasm, Dicer cleaves the pre-miNAs into mature miRNAs. With other proteins, Dicer and argonaute-2 (AGO2) form RISC, which delivers mature miRNAs to their mRNA targets for gene silencing.

including miR-367, is also very high in monkey ESCs [28]. These findings indicate that miRNAs, particularly the miR-302 family, may play a critical role in integrating the regulatory circuitry controlling ESC identity and preventing differentiation during early embryonic development [29].

Several developmental proteins such as Oct4 and Sox2, the two essential reprogramming factors for all iPSC generation methods, are crucial for the transcription of miR-302 in human ESCs or embryonic cells [28,29]. Given that miRNAs modulate the core transcriptional regulatory circuitry of embryonic stem cells [30–32], the ESC-specific miRNAs may play an important role in reprogramming. Conceivably, miR-302, targeting as suppressors of transcription factors essential for cell cycle and differentiation, enhances the activity of Oct4 and results in a perpetual production of miR-302 for the de-differentiation of cancer or somatic cells into iPSCs [7,33,34]. The role of miR-302 on the regulation of cell cycle has also been demonstrated [10,30–32].

On the other hands, miR-302 positively controls the levels of pluripotency biomarkers, including Oct3/4, SSEA-3/4, Sox2, Nonang, and LIN-28 [8,9] and negatively modulates the Nodal inhibitor Lefty [33]. It appears that miR-302 fine-tunes gene expression via the Oct4/Sox2/miR-302-Nodal networks, suggesting that the perturbation in key stem cell miRNA–mRNA networks is a hallmark of maintaining the stem cells.

3. miR-302 and other miRNAs

The embryonic stem cell (ESC)-specific miR-302/367 cluster is located on an intron on the 4q25 region of chromosome 4, transcribed by Pol-II to yield a capped and polyadenylated miRNA precursor that contains three exons and two introns [11,14]. The miR-302 family composes of five members, miR-302b, miR-302c, miR-302a, miR-302d and miR-367. MiR-302a–d have the same seed sequence and, therefore, may target similar 446 mRNAs. The seed of miR-367 is slightly different from that of miR-302a–d but still targets many mRNAs similar to miR-302 (Table 1). Other homologous miRNAs also have been found in hESCs including miR-17/92, miR-371–373, and miR-520 families; however, only the miR-302 family is most abundant in undifferentiated embryonic stem cells and subsequently down-regulated during differentiation [11]. Up-regulation of miR-302 has also been detected in various organ systems in early development and developmental diseases [16,17]; the lack of miR-302 family miRNAs could lead to developmental abnormalities in cardiovascular, gastrointestinal, and neurological disorders, and heart diseases.

Several other miRNAs are associated with the function of the miR-302/367 cluster. MiR-372, together with miR-302, has been demonstrated to silence cyclin-dependent kinase inhibitor 1A (CDKN1A), cell division cycle 2-like 6 (CDK8-like) (CDC2L6), retinoblastoma-like 2 (RBL-2), and TGFBR2, which are responsible for cell cycle and epithelial–mesenchymal transition (EMT), respectively [34]. MiR-200c, miR-368, miR-154*, miR-371, miR-372 and miR-373 family are also highly expressed in hESCs but not in embryonal carcinoma (EC) cells [17]. MiR-302/367 and miR-427, which is ortholog to miR-302/367 cluster in *Xenopus laevis*, were demonstrated to control early embryogenesis of vertebrates through Nodal pathway. It has been shown that miR-427 and miR-430 (miR-302 equivalent in zebrafish) were conserved across vertebrate species and a lack of these miRNAs led to developmental defects in fetuses, especially neurological defects with miR-430, but such effects could be mitigated by miR-302 rescue [16]. MiR-302 has also been shown to play an important role in sex differentiation of embryos. Before sex determination and the establishment of sex organs in fetuses, expression of miR-302d are up-regulated in XY primordial germ cells while significantly lower in XX primordial germ cells [21]. The miR-290–295 cluster codes for a family of miRNAs that are expressed during early embryogenesis and are specific for mouse embryonic stem cells (ESC) and embryonic carcinoma cells (ECC) in mice, which is regulated by cell cycle genes [22]. Interestingly, the vast majority of these embryonic stem-cell-specific miRNAs share, completely or partially, the same seed sequence which is usually the 2nd to 8th segment from 5′ to 3′ end, which are responsible for mRNA targeting specificity (Table 1). Sequence conservation and other embryonic stem cell-specific miRNAs were also listed.

Table 1
Human and mouse embryonic stem cell (ESC)-specific miRNAs.

miRNA	Sequence	Size (Species)	Seed
miR-302b*	acuuuaacauggaagugcuuuc	22 (hsa, mmu)	cuuuaac
miR-302b	uaagugcuuccauguuuuaguag	23 (has, mmu)	aagugcu
miR-302c*	uuuaacauggggguaccugcug	22 (hsa, mmu)	uuaacau
miR-302c	uaagugcuuccauguuucagugg	23 (hsa, mmu)	aagugcu
miR-302a*	acuuaaacguggauguacuugcu	23 (hsa, mmu)	cuuaaac
miR-302a	uaagugcuuccauguuuugguga	23 (hsa, mmu)	aagugcu
miR-302d	uaagugcuuccauguuugagugu	23 (hsa, mmu)	aagugcu
miR-367	aauugcacuuuagcaaugguga	22 (hsa, mmu)	auugcac
miR-17	caaagugcuuacagugcagguag	23 (hsa, mmu)	aaagugc
miR-92a-1	uauugcacuugucccggccugu	22 (hsa, mmu)	auugcac
miR-92a-2	uauugcacuugucccggccugu	22 (hsa, mmu)	auugcac
miR-154*	aaucauacacgguugaccuauu	23 (hsa, mmu)	aucauac
miR-371	acucaaacuguggggggcacu	20 (hsa)	cucaaac
miR-372	aaagugcugcgacauuugagcgu	23 (hsa)	aagugcu
miR-373	gaagugcuucgauuuuggggugu	23 (hsa)	aagugcu
miR-520a-3p	aaagugcuucccuuuggacugu	22 (hsa)	aaagugcu
miR-520b	aaagugcuuccuuuuagaggg	21 (hsa)	aaagugcu
miR-520c-3p	aaagugcuuccuuuuagagggu	22 (hsa)	aaagugcu
miR-200c	uaauacugccggguaaugaugga	23 (hsa)	aauacug
miR-290-3p	aaagugccgccuaguuuuaagccc	23 (mmu)	aagugcc
miR-291-3p	aaagugcuuccacuuugugugc	21 (mmu)	aagugcu
miR-292-3p	aaagugccgccagguuuugagugu	24 (mmu)	aagugcc
miR-293	agugccgcagaguuuguagugu	22 (mmu)	gugccgc
miR-294	aaagugcuucccuuuugugugu	22 (mmu)	aagugcu
miR-295	aaagugcuacuacuuuugagucu	23 (mmu)	aagugcu

Red seed sequence = similar or identical to that of miR-302.
Blue seed sequence = identical to that of miR-367.
*= anti-sense sequences.

4. miRNA-mediated induction of pluripotent stem cells

Previously, we have reported that the miRNAs derived from introns suppressed intracellular RNA homologs and regulate the gene function by packaging human spliceosome-recognition sites along with an exonic insert into an artificial intron [35,36]. We have observed that the splicing and processing of such an exon-containing intron in either sense or antisense conformation produced equivalent gene silencing effects. Using this approach, we have reported that the modulation of tumorigenecity in prostate cancer PC3 cells by constitutive expression of miR-146a [37]. These findings suggest that miR-146a may function as a tumor-suppressor gene in prostate cancer. Subsequently, we have introduced miR-302s to revert human somatic (normal skin keratinocytes and hair melanocytes) and cancer cells (cancerous melanoma Colo-829 and prostate cancer PC3 cells), to become iPSCs, namely miR-302-reprogrammed iPSCs or mirPSCs [7,10,11]. The same phenomenon has been confirmed independently in mice by using miR-294, which has the same seed sequence as miR-302d [38]. The primary advantage of miRNA is direct altering the adult transcriptome and proteome, leading to increased efficiency and decreased time for inducing cell re-direction.

Recently, similar miRNA-mediated reprogramming of somatic cells has also been reported in mouse and human fibroblasts [39–41] using miR-302/367. Other miRNAs such as miR-372 [42] or miR-200c and miR-369 [43], together with miR-302, could also induce iPSC. Interestingly, the combination of miR302, miR-369, and miR-200c were delivered in multiple doses as vector-free gene transfer.

5. Mechanisms of miR-302/367-mediated reprogramming

Reprogramming via miR-302/367 is probably mediated through its targeting of various cell development genes (Fig. 2). Given that a single miRNA targets several and hundreds of mRNAs, we propose that miR-302/367-mediated reprogramming is mediated through at least three pathways. Understandably, more studies in the future will provide a clear mechanism by which miR-302, alone or with other ESC-specific miRNAs, carries out the reprogramming in a more integrated networking.

First, miR-302 targets various epigenetic factors leading to global demethylation in target cells [7,11,44]. DNA demethylation commonly occurs after fertilization at the 1–8 cell stage or a few days after the development of premordial stem cells. In the zygote, global demethylation takes place at the promoter binding site of several ESC specific transcription factors, resulting in preservation of imprinting. The reprogramming of somatic cell may acquire unique characteristics of pluripotency and undifferentiated status similar to those of embryonic stem cells by using the same mechanism. Indeed, miR-302 silences lysine-specific histone demethylases 1 and 2 (AOF1 and AOF2) and methyl-CpG binding proteins 1 and 2 (MECP1-p66 and MECP2); the down-regulation of these important epigenetic genes destabilizes DNA methyltransferase 1 (DNMT1) which leads to genome wide demethylation and consequently facilitates reprogramming and iPSC development [8,11]. The deficiency of DNMT1 activity further suppresses the methylation of newly replicated DNA in S-phase of the cell cycle and consequently passive demethylation takes place and daughter cell genomes are demethylated and reprogrammed [45]. Indeed, silencing AOF2 enhanced global demethylation during reprogramming of human hair follicle cells by miR-302s [11].

Second, miR-302 and Oct3/4, Sox2, Nanog, and others form a reciprocal positive feedback in the miR-302/367 transfected cells. Indeed, miR-302 inhibits NR2F2 (COUP-TFII, a member of the nuclear orphan receptor family of transcriptional repressors) expression [34], which prevents the inhibition of Oct4 expression by NR2F2 at the post-transcriptional level [30], As a result, miR-302 increased expression of Oct4, Nanog, and Sox2, which were

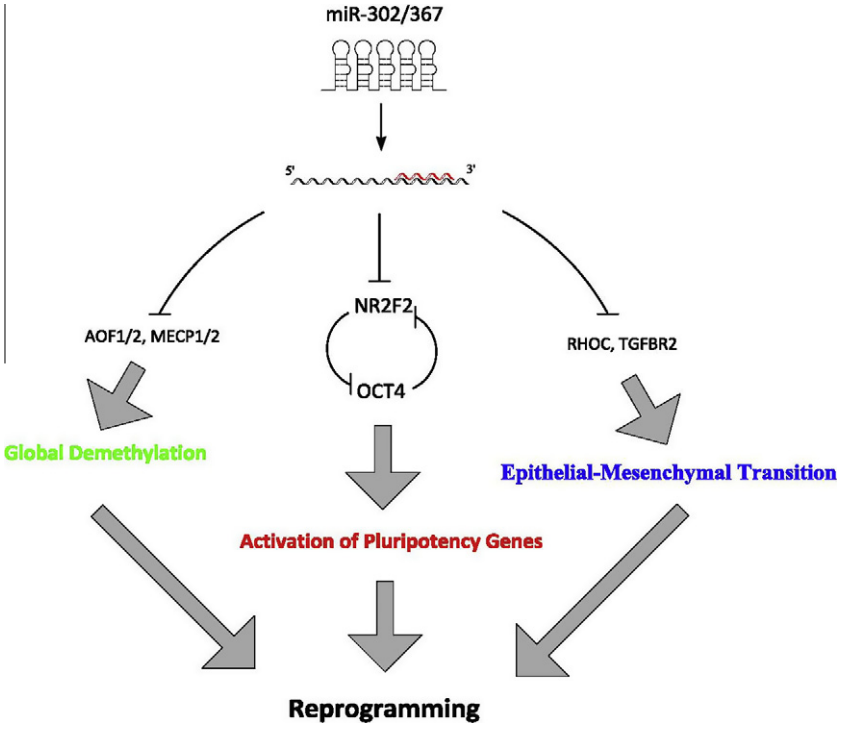

Fig. 2. Mechanism of miR-302/367 mediated reprogramming. Successful reprogramming is involved at least in the following three pathways. The miR-302/367 targets MECP1/2 and AOF1/2 and silences their expression, which causes the reduction of various downstream molecules such as DNMT1, resulting in global demethylation. Concurrently, miR-302/367 also represses the expression of suppressor gene NR2F2 and possibly other transcriptional repressor genes to activate OCT4 expression. The activation of OCT4 and other pluripotent genes, in turn, can inhibit NR2F2 and stimulate miR-302/367 production. These series of processing eventually result in the activation of other genes that are important in maintaining pluripotency and reprogramming. Meanwhile, miR-302/367 silences RHOC and TGFβR2 expression and the downregulation of these epithelial–mesenchymal transition (EMT), enhancing the reprogramming process.

observed in induced pluripotent stem cells (iPSCs) when the level of miR-302 was 1.1–1.3-folds of that in normal human ESCs [11]. Further, Oct 4 activates the level of miR-302 [29,30,33], which, in turn, stimulated Oct 4 and other transcriptional factors, Thus, a reciprocal positive loop between miR-302/367 and Oct4, Sox2, Nanog and other factors such as inhibition of miR-302 by the Nodal inhibitor Lefty [34] maintains the pluripotent status of the ESC [46]. In the same manner, the reprogramming with Oct4, Nanog, Sox2 and other factors stimulates the level of miR-302, silences epigenetic factors, then suppresses NR2F2, and further stimulates ESC-specific genes such as Oct4, Sox, and other transcriptional factors [34].

Third, miR-302 also targets the transforming growth factor, beta receptor II (TGFBR2) and ras homolog gene family, member C (RHOC) genes, which facilitate epithelial–mesenchymal transition (EMT). MiR-302 inhibits TGFBR2 and RHOC expression, resulting in the reversal of the EMT occurring during the early reprogramming process, probably via the regulation of the TGFβ/Nodal/Smad-2/3 pathway [42]. Silencing TGFBR2 and RHOC by using siRNA or other inhibitors has been shown to facilitate the conventional reprogramming of somatic cells using the four factors [41,47,48]. On the other hand, miR-302/367 promotes bone morphogenetic protein (BMP) signaling by targeting BMP inhibitors transducer of erbB-2 (TOB2), DAZ associated protein 2 (DaZAp2), and SLAIN motif family, member 1(SLAIN1) [41]. It is highly likely a complicated networking among the numerous members of the TGFβ superfamily, including TGFβ, activin, BMP, Lefty, Cripto, and others are involved in integrating the control of miR-302/367-mediated reprogramming.

Although various embryonic stem cell-specific miRNAs have been found to induce somatic cell reprogramming in combination with miR-302, the miR-302 family seems to be an essential component for successful reprogramming [7,10,11,39–43].

6. Anti-tumor activity in miR-302-mediated iPS

Human embryonic stem cells (hESCs) and iPSCs usually show teratoma, which may develop to tumors. The miR-302/367-mediated iPSCs (mirPSCs) appears to be tumor-free [10,49], suggesting that miR-302 contains self-regulating anti-tumor effects. Interesting, miR-302 inhibits the tumorigenicity of human pluripotent stem cells by enhancing multiple G1 phase arrest pathways [10] because the miR-302 family hinders the progression of G1 phase and blocks G1 to S cell cycle transition by targeting the co-suppression of cyclin dependent kinase 4/6 (CDK4/6) and cyclin dependent kinase 2 (CDK2) in human normal hair follicle and cancerous MCF-7 cells [10]. Extensive apoptosis was only observed in cancer but not normal cells after ectopic expression of only the miR-302 family but not miR-367. This result matches previous studies [7] showing that miR-302 induces significant programmed cell death (apoptosis) in more than 98% of cancer cells while reprogramming about 2% cells to form iPSCs. Both studies strongly suggest the anti-tumorigenicity effect of miR-302. Notably, polycomb ring finger oncogene (BMI1), an oncogene that is highly expressed in cancer stem cells, was experimentally found to be a target of miR-302 as well, indicating the involvement of miR-302 in the prevention of cancer development and tumor formation [10].

Yet, unlike other ESC-specific miRNAs, the expression of mir-302/367 family was also detected in malignant germ cell tumors and yolk sac tumors and may be responsible for the immortalization of tumor cells similar to the unlimited proliferative capacity in ESC and iPSC [20,50]. For example, miR-302/367 has been observed in malignant testicular germline cells, inversely correlating with the expression of P63 tumor suppressor gene. When miR-302/367 is reduced in testicular germ cell tumor, the expression of P63 protein and mRNA rise significantly [50]. Since P63 activates apoptosis, it is thought that miR-302/367-mediated suppression of P63

is instrumental in the self-renewal and prevention of apoptosis in both embryonic stem cells and cancer cells. Nevertheless, this contradicting observation is likely due to insufficient concentration of miR-302 in cancer tissues and the presence of other oncogenic miRNAs (onco-miRs) such as miR-372/373, as it has been shown that more than 1.1–1.3-folds miR-302 level of that in hESCs is required for inducing the reprogramming process and preventing the stem cell tumorigenicity [10].

Judging from the fact that miR-302/367 drastically affects self-renewal and infiltration properties of glioma-initiating cells through CXCR-4, an alpha-chemokine receptor specific for stromal-derived-factor-1 (SDF-1 also called CXCL12), which is endowed with potent chemotactic activity for lymphocytes [49], it is curious to determine whether these miRNAs have effects on inflammation and tumor-initiating cells in general. Given that miR-302/367 or miR-302/372 reverses the TGFβ-blocked epithelial-to-mesenchymal transition [40,42] by mediating through the modulation of the level of Lefties which regulates the TGFβ/Nodal pathway [42] or by promoting E-cadherin expression and colony formation [40], the role of miR-302 and its associated miRNAs as agents for metastasis of cancer cells remains to be elucidated.

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