



The Effect of mi-RNAs in the Progress or Inhibition of Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal Stromal Tumor is considered as one of the rare tumors in the gastrointestinal tract and is mainly found in the gastrointestinal lining and the interstitial cells of Cajal, more than half of which arise in the stomach and the rest do in the small intestine and along the gastrointestinal tract. Nowadays, the major role of micro-RNAs is known for any researcher. Our studies show that micro-RNAs, which play an interfering role in the molecular processes, can have significant destructive or very efficient and beneficial impact on all the stages from inception to final treatment. This overview article deals with the various micro-RNAs impacting on this tumor from different aspects and finally offers the best mi-RNA in terms of its properties.

Introduction

Gastrointestinal Stromal Tumors (GISTs) are like an abscess in the stomach lining [1], that represent about 1% of total cancer cases and are clinically considered as the sub epithelial lesions. While, its common areas for incidence are stomach and a small part of the intestine, but this tumor may be developed and expanded in any part of the gastrointestinal tract [2]. The incidence abundance of these mesenchyme tumors is 10 to 15 new cases per million people in a year. Most of these tumors are developed by the activating mutations in the *KIT* genes which cause 80% - 85% and in the *PDGFRA* genes which cause 5% - 7% of the tumor cases [3]. The receptor tyrosine kinase type 3 (RTK), (CD117), and myeloid of the variable marker [4] or neuronal features are expressed by 95% of the GISTs. A major part of the GISTs represent the activating mutations in the *KIT* gene or in the receptors associating with the platelets derived from the growth factor receptor of alpha (*PDGFRA*) and the mutations available in these two genes are mutually exclusive [5].

In terms of incidence area, these tumor types are more common in the stomach (about 60%) and, as mentioned previously, they may also appear in the small intestine as the second area (about 30%). The other parts of the digestive tract are less likely to involve in this disease. Only 5% of the GISTs have been found in the colon and less than 5% in the esophagus. In some cases, the primary site of the stromal tumor is on the outside of the gastrointestinal tract and behind the peritoneum which is described for less than 10% of the diagnosed cases [6].

A small proportion of the GISTs have been observed at the areas outside of the gastrointestinal tract, like Mesentery, Peritoneum, and especially, Omentum [7]. On the other hand, the micro-RNAs play an important role in tumorigenesis and it is observed that the abnormalities in the adjustment of micro RNAs (mi-RNAs) are related to many of the diseases such as cancer [8,9]. Micro RNAs are the small and single-stranded non-coding RNAs (approximately 20-22 nucleotides) which adjust the target gene expression through binding to the complementary areas (seed sequences) in the target gene's mi-RNA [10]. About 30% of the human genes' expression is estimated to be adjusted by mi-RNAs. The mi-RNA synthesis is done by Drosha and Dicer key enzymes, which is basically dependent on the mi-RNA/m-RNA interaction and causing RNA or RISC induced silencing complex [11]. Normally, mi-RNAs are transcribed by RNA polymerase II; the same enzyme synthesizing the cellular mRNAs' transcription. The primary mi-RNA, similar to the cellular mRNAs, has a warhead at the end of 5-prime and a polyadenylate tail at the end of 3-prime [12]. In addition, by the RNase III and Drosha enzyme complexes that are attached to its adjustment subunit, they can be converted into the primary mi-RNAs [13].

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Received Date: 07 Feb 2018

Accepted Date: 15 Mar 2018

Published Date: 19 Apr 2018

Citation:

Ardehkhani S, Kormi SMA, Azizi A. The Effect of mi-RNAs in the Progress or Inhibition of Gastrointestinal Stromal Tumors. *Clin Oncol*. 2018; 3: 1445.

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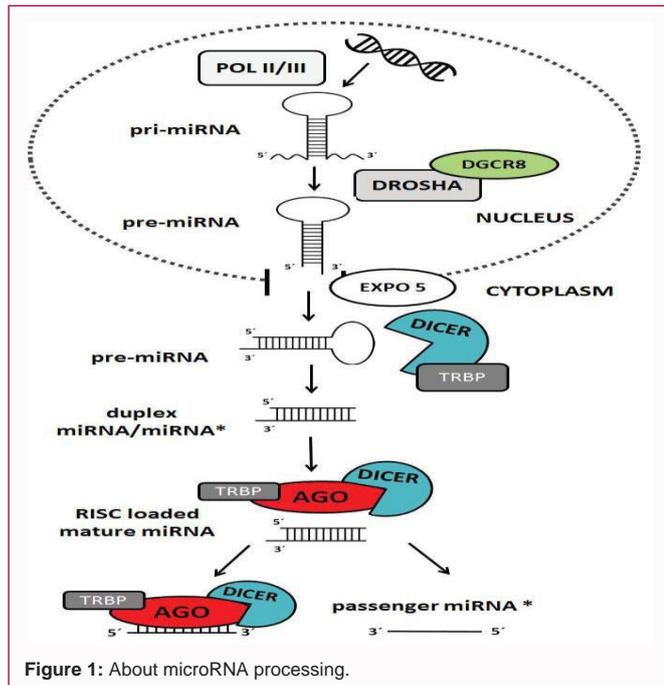


Figure 1: About microRNA processing.

The mi-RNAs synthesis steps are continued through the activity of the trimming enzymes on the leading double-stranded mi-RNAs. These reactions occur in the core through the activities of an enzyme called Drosha and in the cytosol by the activity of the enzyme Dicer1. Mi-RNAs play an accurate role in the changes in gene expression, as a dimer [14]. Mi-RNAs play also a highly accurate role in the genes' switching and expression, as the adjustor bio-molecules [15].

Currently, there is a variety of drugs being used for the GIST treatment, including Sorafenib, Imatinib, Sunitinib, and Nilotinib [16].

The progressed GISTs (non-resectable and/or metastatic) are resistant to conventional chemotherapy [17], but instead, sensitive to the Tyrosine Kinase Inhibitors (TKIs), Imatinib, and Sunitinib. Currently, 400 mg/day of Imatinib is used for the worldwide standard first-level treatment of the progressed GISTs [18].

The Imatinib drug is used for treatment when the *KIT*/*PDGFRA* mutations are specifically detected. In addition, there are many different strategies that can be applied for recovery, such as increasing the dosage of Imatinib from 400 mg to 800 mg per day, surgically removal of the progressive lesion's focus area, and the treatment by Sunitinib malate and Regorafenib (both are the multi-purpose tyrosine kinase inhibitors having anti-angiogenesis properties) which are the drugs recorded for the second and third level, respectively [19].

Discussion

Nowadays, the importance of mi-RNAs in tumor progression or suppression is an obvious thing for the people. As mentioned earlier, there are various mi-RNAs involved in gastrointestinal stromal tumor and the list is increasingly being grown every day, the most important among which are as follows:

Mi-RNA-21

Mi-RNA-21 has been reported as a negative regulator of the tumor suppressors by targeting *Bcl-2*; and so, it may operate as a

potent inhibitor of the tumor as well as the induction of apoptosis [22] in the GIST cells. In addition, the development of mi-RNA-21 can cause an increased sensitivity to Imatinib in the GIST cells which represents a potential role in the GIST treatment [23].

In accordance with the various studies carried out, the mRNA level associating with *Bcl-2* was significantly up-regulated in the GIST samples [22].

The observations indicated that the *Bcl-2* gene mi-RNA-21 levels (with β -act in as an internal reference gene) increased in the GIST cells. This gene that encodes the pri-mi-R-21 (the primary transcript consisting of mi-RNA21) is placed within the *TMEM49* gene intron area. Despite the overlapping of pri-mi-R-21 and *TMEM49* in the same transcription direction, pri-mi-R-21 is independently transcribed by its own promoter regions and ends in its own poly (A) tail. After transcription, pri-mi-R-21 is finally processed to become mature mi-R-21. The mi-R-21 was exposed to over-expression in almost all cancer types and thus, was classified as an Onco-miR. Despite the fact that pri-mi-R-21 has a promotional area for its own, but it has been found that mi-R-21 is subjected to up-regulation in many pathological conditions such as cancer. There has been proposed a non-transcriptional mechanism for up-regulating the mi-R-21 gene proliferation instead of over-activating the promoter. However, many of the available data indicate that the regulation of the mi-R-21 expression continues in the transcription process and the post-transcription level. The pri-mi-R-21 potent promoter areas have been fully investigated but, there is still much discussion about the actual size of pri-mi-R-21, the Transcription Start Site (TSS), and the minimal promoter of pri-mi-R-21 [24].

Mi-RNA-518a-5p

Mi-RNA-518a-5p decreases the proliferation rate and increases apoptosis in 822R. The low expression of mi-RNA-518a-5p is likely to increase the *PIK3C2A* expression and affect the cellular response to the drugs. *PIK3C2A* is a specific gene target for mi-RNA-518a-5p in the GISTs resistant to Imatinib mesylate. The micro-error analyses showed that mi-RNA-518a-5p found in the cells of the GISTs resistant to Imatinib were subjected to a decrease in the expression and such a decrease in the expression of mi-RNA-518a-5p has been verified through the Real-Time PCR methods and the mi-RNA micro-error results [25].

Mi-RNA-221/222

There have been various experiments and studies performed and it was found that when these mi-RNAs were displaced to the GIST48, the cells represented important effects in the various cellular processes in association with the role of every *KIT* gene in the tumor development (such as migration, cell proliferation, and apoptosis).

Therefore, mi-RNA-221/222 may be applied as an alternative therapeutic option for GIST.

Additionally, there have been some strategies made for overcoming the drug resistance concerns [26].

Mi-RNA-137

Using In-Silico analysis, it was revealed that the gene *TWIST1*, as a key regulatory gene for the gene *EMT*, can be considered as a target for mi-RNA-137.

The expression of mi-RNA-137 decreases dramatically in the clinical samples of GIST.

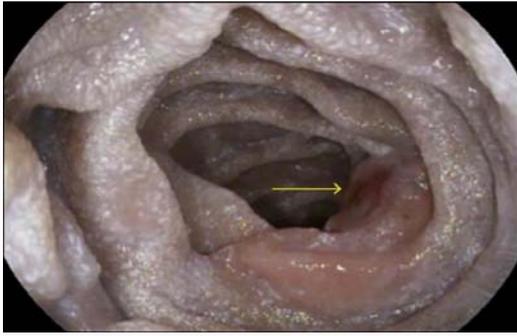


Figure 2: Endoscopic appearance of 8 mm superficial ulcer in the second portion of the duodenum [20].



Figure 3: Imaging revealed an approximately 10 cm mass in the stomach near the fundus [21].

Using the quantitative RT-PCR and Western blot methods, it was confirmed that mi-RNA-137 has a direct operation on the *TWIST1* gene in the GISTH1 cells (the gastrointestinal stromal tumor of human cell line) and suppresses the expression of the above gene in this tumor [27].

Mi-RNA-137 enhances the expression of E-cadherin and cytokeratin, and in contrast, suppresses the expression of N-cadherin and vimentin that play an important role in the cancer cells' migration and start of metastasis [27,28,29].

The *in vitro* analyses showed that mi-RNA-137 causes an increased morphology of the epithelial cells, a decreased migration in the GIST cells, prevention of G1 cell cycle's activation, and the apoptosis induction.

Therefore, mi-RNA-137 can operate as an anti-migration and anti-metastatic factor in the GIST and our studies provide a potential approach to promoting the mi-RNA-137 based therapeutic strategies for GIST.

This is worth to note that mi-RNA-137 is one of the mi-RNAs with different expression in the GIST cells and could be considered as a negative biomarker to diagnosis.

As mentioned previously, the over expression of mi-RNA-137 increases the expression of E-cadherin and cytokeratin, and inhibits the expression of N-cadherin and vimentin in the GIST cells, in contrast [27].

Mi-RNA-218

Mi-RNA-218 causes a negative regulation of the expression of the *KIT* protein and inhibits the GIST cells' proliferation and migration.

Using quantitative RT-PCR, the expression of mi-RNA-218 in various tissues, especially the tissues adjacent the GISTs and the GIST cell lines including GIST882, GIST430, GIST48, and GIST-T1 were studied and also, by the flow cytometric approach, the effect of mi-RNA-218 on the proliferation and apoptosis of the GIST-T1 cell was identified.

Transwell invasion chamber was applied for detecting the effect of mi-RNA-218 on the GIST1 cells' migration.

MTT assay showed that the over expression of mi-RNA-218 in the GIST-T1 cells reduces the survival ability of the tumor cells, significantly; which is a promising new therapeutic approach [30].

Mi-RNA-210

Mi-RNA-210 is considered as a regulating key responding to hypoxia. Mi-RNA-210 is found much more in the muted-SDHx or -*VHL* of PC/PGLs (7.6 folds) rather than the tumors lacking SDHx or lacking the VHL mutations. Numerous analyses indicate that the increased expression of mi-RNA-210 has a significant relationship with SDHx or the VHL mutations and a little relationship with the malignancies.

Mi-RNA-210 expression level in the malignant tumors PC/PGLs (PZ0.05) is much more rather than in the benign ones, but this is of less importance when the uncommon tumors compound with the benign ones (PZ0.08).

The mi-RNA-210 level is higher in the tumors with a deficiency in SDH (an average of 2.58) as compared with those having enough and appropriate SDH (an average of 0.60; PZ0.0078).

The mi-RNA-210 level is higher in the diseases derived from the neurosphere cell lines involving the SDHB mutations (-6.5 units incremented) as compared with the normal controls under the normoxic conditions.

The over expression of mi-RNA-210 in PC associating with PGL, SDH, and GISTs proves the inappropriate role of the hypoxic cellular responses in these tumors' development, more [31].

Mi-RNA-320a

The low expression of mi-RNA-320a is associated with the short-term resistance to Imatinib and introduces a potential mechanism for sustainability of Imatinib. There are 13 genes with different expressions for the primary GISTs and the GISTs resistant to Imatinib among which, mi-RNA-320a in the GISTs resistant to Imatinib has a lower expression (P ¼ 0.018). Therefore, it can be said that mi-RNA-320a may be involved in the Imatinib resistance process.

Also, the down-regulated mi-RNA-320a can suppress the proliferation and migration of the tumor cells in many cancer types such as colon cancer and liver cell cancer.

Another study suggests that there may be an association between mi-RNA-320a and chemotherapy [17] of the colorectal cancer cells. In this study, it was found that mi-RNA-320a observed in the GISTs resistant to Imatinib was down-regulated and there is an association between the low expression of mi-RNA-320a and short sized TTR.

There are many genes targeted by mi-RNA-320a and down-regulation of mi-RNA may suppress the GIST cells' apoptosis is one of the target genes of mi-RNA-320a and can induce the change in *ABC1*, one of the genes associating with drug resistance [32].

Table 1: Characterized features of each mi-RNA.

Mi-RNA type	Effects and roles
21	Tumor inhibition and apoptosis induction through inhibition of <i>Bcl2</i> , increasing the sensitivity to imatinib
518a-5p	Inhibition of the proliferation and increasing the apoptosis and decreasing the drug resistant gene <i>PIK3C2A</i> expression
221\222	Critical effects on the apoptosis processes, cell migration and –proliferation, alternative therapeutic option for GIST
137	Suppressing the <i>TWIST1</i> gene expression, increasing the E-cadherin and cytokeratin, reducing the N-cadherin and vimentin, preventing the metastasis, inducing the apoptosis, reducing the migration, negative biomarker, different expression in the GIST cells
218	Reducing the Pr- <i>KIT</i> expression, inhibition of proliferation and migration, reducing the tumor cells survival
210	The setup key responding to hypoxia, high-level expression in the malignant tumors
320a	Short time resistance to imatinib, inhibiting the proliferation and migration of colon and liver tumor cells, inhibition of apoptosis, induction of gene expression associated with ABC1B drug resistance
494	Adverse effect on the expression of gene <i>KIT</i> , effect on the AKT and STATE3 signal transduction pathway
196a	Participating in the tumor development, involved in the expression of the metastasis-associated gene, inhibition of the gene <i>HOXC8</i> expression, inhibition of invasion and metastasis, opposite effects in different tumors
133b	Down regulated in the carcinoma of the bladder, colon, lung, and esophagus; direct targeting of the gene <i>FASCIN1</i> by m-RNA; adverse effect of expression by mitotic divisions
17-92	Associating with the expression of the genes located at 13q31.3 in the advanced GIST, proliferation inhibition, apoptosis induction, beneficial effect on the imatinib-resistant patients
125a-5p	Imatinib associated stability, adverse effect on the <i>PTPN18</i> gene expression
34a-335	Inhibition of cell proliferation, inhibition of migration and invasion, targeting the <i>PDGFKA</i> gene, inhibition of tumorigenesis by epigenetic processes

Mi-RNA-494

The quantitative RT-PCR method is used for evaluation of mi-RNA-494 expression levels, western blot for evaluating the *KIT* protein expression levels and measuring by the enzyme luciferase for evaluating the target.

The functional effect of mi-RNA-494 on the GIST882 cells (GIST cell lines with the muted *KIT* gene activity) was proved by evaluating the cells' proliferation and the categorization of the cells activated by fluorescence was analyzed.

The direct targeting of the *KIT* gene by mi-RNA-494 was shown by reduction in the *KIT* gene expression after mi-RNA-494 over expression and increase in the *KIT* gene expression after inhibition endogenous mi-RNA-494 expression.

Mi-RNA-494 regulates the *KIT* gene through binding to two different connection points.

The over expression induction in GIST882 reduces the expression of downstream molecules in the *kit* gene signal transduction pathways [33] consisting of the phosphor-AKT and phosphor-STAT3 [34].

Mi-RNA-494 is a negative regulator of *KIT* gene in the GISTs and its over expression in the GISTs may increase the hopes for the GIST treatment [35].

Mi-RNA-196a

This type of mi-RNA contributes in the tumors' development and is associated with the high-grade and metastatic tumors and those samples having a low capability of survival and being alive in the GIST samples.

The mi-RNA-196a gene is placed into *HOX* gene clusters and the micro-error expression analysis shows that the genes *HOX* and *HOTAIR* are up-regulated consistently in the GISTs with a high expression of mi-RNA-196a. These findings indicate the very high and simultaneous expression of the *HOX* genes with the non-coding RNAs in the human cancers which show that the genes mi-RNA-196a and *HOTAIR* are two efficient biomarkers being the treatment targets in the malignant GIST cells.

The up-regulation of mi-RNA-196a has a strong relationship

with the high risk in the GIST developed patients. In addition, the mi-RNA-196a over-expression is associated with the up-regulation of the *HOXC* cluster genes and a non-coding RNA relating to the metastasis in the GISTs. The mi-RNA-196a high expression has been observed in both the small intestine and gastric GIST.

Mi-RNA-196a and *HOTAIR* are expressed in the GIST-T1 cells. The micro-error results showed that mi-RNA-196a is expressed in the high-risk GISTs significantly more than the other groups. The micro-error data analysis for the mi-RNA-196a target genes was computationally predicted through target scan.

In addition, mi-RNA-196a inhibits the *HOXC8* gene expression and prevents the invasion and metastasis of the breast cancer cells [36].

Mi-RNA-196a seems to apply the opposite effects on the tumors with various origins [37].

Mi-RNA-133b

Mi-RNA-133b is placed in the 6p12.2 area and is down-regulated in the Bladder, Colon, Lung, and Esophagus carcinomas.

This type of mi-RNA is down-regulated in the high-grade GISTs; in contrast, the fascin-1 mRNA is up-regulated as compared with mi-RNA-133b. This result is consistent with the previous report suggesting that fascin-1 may be a direct target of mi-RNA-133b.

The mi-RNA-133b expression tends to decrease in the GISTs with the high-grades of NIH as compared to those with the grades lower than medium and its expression level is inversely related to the mitotic division's number.

When the mi-RNA-133b down-regulation occurs in the cancerous cells, an up-regulation seems to occur in the target mRNA and thus, it can involve in the oncoprotein over expression or activity.

The findings also indicated that the primary location, tumor size, AFIP grade and genotype of the *KIT* gene have no relationship with mi-RNA-133b expression level [38].

Mi-RNA-17-92

The mi-RNA-221/222 and mi-RNA-17-92 cluster members decrease dramatically (Po0.01) in the GISTs vs. GI-LMS and the

normal gastrointestinal tract control tissues. The progressed GIST has been observed to be associated with the reduced mi-RNA-17 and mi-RNA-20a having some genes in 13q31.3.

Over-expression of mi-RNA-17/20a/222 in the GIST cell lines leads to the serious inhibition of the cellular proliferation, affection on the cell cycle process, apoptosis induction, and a strong down-regulated protein in a lower level- and the mRNA levels of their *ETV1* and *KIT* predicted target genes. The analyses reporting the enzyme luciferase approve direct regulation of the genes *KIT* and *ETV1* by mi-RNA-222 and mi-RNA-17/20a, respectively.

There is a certain potential in the mi-RNA-17/20a/222 targeting the genes *KIT* and *ETV1*. This mi-RNAs' transference as the drug can be a potential option for managing the GISTs especially in the patients resistant to Imatinib. Both *KIT* genes' structure contains the potential parts for connection to mi-RNA-17/20 and mi-RNA-222.

The GIST-T1 and GIST-882 cells lines are transferred as the mimics of the mixed mi-RNA-20a, mi-RNA-17, and mi-RNA-222 (Mneg).

The mi-RNA-17-92 and mi-RNA-221/222 cluster members distinguish the GISTs from GL-LMS [39].

Mi-RNA-125a-5p

The over expression of mi-RNA-125a-5p and mi-RNA-107 is associated with the Imatinib's sustainability in the GIST samples. The over expression of mi-RNA-125a-5p inhibits the *PTPN18* expression and this inhibition increases the survival capability of the GIST882 cells being treated by Imatinib. The *PTPN18* protein levels are significantly lower in the GISTs resistant to Imatinib and have an inverse relationship with the expression of mi-RNA-125a-5p. The new findings show a new functional role for mi-RNA-125a-5p about responding to Imatinib through regulating the *PTPN18* in the GISTs.

The mi-RNA-125a-5p modifies the Imatinib sensitivity in the GIST882 cells having a homozygous mutation in the *KIT* gene but plays no role in the GIST48 cells having a dual mutation in the *KIT* gene.

In addition, the functional role of mi-RNA-125a-5p and its potential targets in the GIST cells' drug resistance was examined and the target protein expression level in the GIST clinical samples was evaluated [40].

Mi-RNA-335 and mi-RNA-34a

The CpG islands in the mi-RNA-34a and mi-RNA-335 are repeatedly methylated in the GIST-T1 cells and primary GIST samples [41]. However, these CpG islands are not methylated in the normal mode and the methylation of these areas has a direct relationship with the target gene silence [42,43].

The transfer of the mi-RNA-34a or mi-RNA-335 molecules, which are somewhat similar to each other, into the GIST-T1 cells, inhibits the cell proliferation and also, mi-RNA-34a is considered as an inhibitor of migration and invasion of the GIST-T1 cells.

One of the target genes being down-regulated through mi-RNA-34a has been predicted to be the *PDGFRA* gene.

The intervening RNA knocked down for the gene *PDGFRA* in the GIST-T1 cells inhibits cell proliferation and it is suggested that the inhibitory impact of mi-RNA-34a tumor is applied by targeting the gene *PDGFRA* through RNA, at least at this part [34]. *PDGFRA* gene

expression inhibition by mi-RNA-34a through mainly RT-PCR and slightly GIST-T1 cells has been approved.

Mi-RNA-34a and mi-RNA-33 are considered as two candidates among the mi-RNAs to inhibit tumorigenesis in the GIST cells and are included in many factors silencing the genes through epigenetic processes in the GISTs [41,44].

Results

In this article, we have reviewed the various characteristics of the mi-RNAs effecting on the GIST disease. These characteristics include tumor inhibition and suppression, therapeutic effects, cell proliferation, cell division inhibition (in my opinion, division and proliferation make the same sense and it is better to write only one of them), migration, drug resistance, drug delivery, response to hypoxia, effect on the gene expression, capability to be methylated, metastasis ability, apoptosis ability. Certainly, every mi-RNA does not have necessarily all the above-mentioned features but the characterized features of each mi-RNA are listed in (Table 1). A mi-RNA is characteristically useful when it plays an effective role in terms of therapeutic interventions, drug delivery, apoptosis induction, and disease control. Comparing all the above-mentioned mi-RNAs, mi-RNA-21 seems to have a better interfering effect than the RNAs because it is directly involved in the inhibition of carcinogenesis. Further, it plays an effective role in treating this disease by increasing the sensitivity of the cells to Imatinib and apoptosis induction, although additional and more accurate research is required to better understand the control and mechanism of the effect of this mi-RNA.

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