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Targeting miRNA for therapy of juvenile and adult diabetic cardiomyopathy

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Abstract

Prevalence of diabetes mellitus (DM), a multifactorial disease often diagnosed with high blood glucose levels, is rapidly increasing in the world. Association of DM with multi-organ dysfunction including cardiomyopathy makes it a leading cause of morbidity and mortality. There are two major types of DM: type 1 DM (T1D) and type 2 DM (T2D). T1D is diagnosed by reduced levels of insulin and high levels of glucose in the blood. It is caused due to pancreatic beta cell destruction/loss, and mostly found in juveniles (juvenile DM). T2D is diagnosed by increased levels of insulin and glucose in the blood. It is caused due to insulin receptor dysfunction, and mostly found in the adults (adult DM). Both T1D and T2D impair cardiac muscle function, which is referred to as diabetic cardiomyopathy. We and others have reported that miRNAs, a novel class of tiny non-coding regulatory RNAs, are differentially expressed in the diabetic heart and they contribute to diabetic cardiomyopathy. Here, we elaborated the biogenesis of miRNA, how miRNA regulates a gene, cardioprotective roles of different miRNAs including miRNAs present in exosomes, underlying molecular mechanisms by which miRNA ameliorates diabetic cardiomyopathy, and the role of miRNA as a potential therapeutic target for juvenile and adult diabetic cardiomyopathy.

Keywords

Diabetic heart; T1D; T2D; miRNA; exosome

1. Introduction

Diabetes mellitus (DM) is a rapidly increasing menace throughout the world (1, 2). It is associated with multi-organ disorders (3, 4), including cardiovascular disease (5, 6). Despite current therapeutic strategies, prevalence of diabetes-mediated cardiomyopathy has markedly increased (7, 8). Considering the increasing trend for prevalence of DM in the world (9), this number is projected to be higher in future. Therefore, a novel therapeutic strategy is warranted to ameliorate diabetic cardiomyopathy. Recent studies revealed that microRNA (miRNA) is a novel class of non-coding RNA, which is endogenously

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biosynthesized and regulates gene expression (10). Empirical evidences demonstrate that miRNA has potential to mitigate/prevent pathological remodeling in various diseases (11–15), which makes it an attractive therapeutic target for various diseases. As per the Clinicaltrials.gov website, to date there are more than 300 clinical trials on miRNA for different diseases, including anti-miR-122 for Hepatitis C (clinicaltrails.gov # NCT01200420), and miR-34 mimic for primary liver cancer and solid tumors (clinicaltrials.gov #NCT01829971). MiRNA is also emerging as a novel therapeutic target for cardiovascular diseases (16, 17), and diabetic cardiomyopathy (18–20). It is reported that several miRNAs are differentially expressed in the diabetic heart (21–25). Restoring the levels of specific miRNA in the diabetic heart may have therapeutic benefits. For example, miR-133a is downregulated in the diabetic heart (21, 26), and miR-133a mimic treatment to the diabetic heart improves contractility and ameliorates diabetic cardiomyopathy (27). MiRNAs are also present in an exosome, a small vesicle formed by inward folding of cell membrane. Exosomes are secreted from cardiomyocytes (28) and cardiac progenitor cells (29), and play a crucial role in cardiac remodeling (30–33). This chapter embodies the role of miRNA in mitigating diabetic cardiomyopathy in juvenile and adult hearts.

2. Diabetes Mellitus

i) Background

DM is often diagnosed by an elevated blood glucose levels (fasting blood glucose level is higher than 120mg/dL). The normal fasting blood glucose level in humans is 80mg/dL. When the fasting blood glucose level ranges between >80 and <120 mg/dL, it is considered a pre-diabetic condition. In addition to increase in prevalence of DM population (1, 2), the number of pre-diabetic population is also rapidly increasing (34). DM is a complex disease with metabolic disorder and multiple etiology (4, 35). Despite insulin treatment to lower the blood glucose level especially in T1D, and metformin drug treatment to improve insulin sensitivity especially in T2D there are numerous incidence of morbidity and mortality in DM patients, which is corroborated in several clinical trials including Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), and Veterans' Administration Diabetes (VADT) (36). Therefore, novel therapeutic strategies are warranted to ameliorate diabetic cardiomyopathy.

ii) Types of Diabetes Mellitus

Based on insulin levels in the blood, DM is categorized into two major types: type 1 DM (T1D) and type 2 DM (T2D). In T1D the pancreatic beta cells, which biosynthesize and secretes insulin, are either less in number or non-functional that results in decreased insulin production and/ or secretion in the blood. Reduced insulin levels in the blood compromise glucose uptake and metabolism that result in elevated blood glucose level. T1D is mostly prevalent in young individual and that is why they are also called juvenile DM. In T2D the pancreatic beta cells are functional and release insulin in the blood but circulating insulin is unable to inter a cell due to impaired insulin receptor function or insulin insensitivity. It results in accumulation of insulin in the blood. Therefore, in T2D both insulin and glucose levels are high in the blood. T2D are mostly prevalent in the adults. Besides T1D and T2D there is a third type of DM, which is present during gestation/pregnancy and it is called

gestational DM. This DM is present only during gestation and after delivery of the baby blood glucose level is normalized. Pre-diabetes can be categorized as the fourth type of DM, however, it may progress to either T1D/T2D or revert to normal blood glucose levels (37).

iii) Diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is a disease of heart muscle which leads to heart failure. It is defined as heart failure caused due to DM without any symptoms of hypertension, coronary artery disease, valvular disease, or ischemia (38). DCM is categorized into three types: early stage where the changes are mostly at molecular levels such as altered calcium homeostasis, depleted glucose transporters GLUT1 and GLUT4, middle stage where the changes are also observed at structural levels such as increased size of left ventricle and cardiac fibrosis, and functional levels such as diastolic dysfunction, and late stage where besides molecular and structural changes both diastolic and systolic functions are compromised (39). DM contributes to micro-, and macro-vascular complications (34, 40–42), and increases the chances of heart failure 2–4 folds as compared to age and gender matched non-diabetic individuals (43, 44). The molecular mechanisms underlying DCM and the predictors and prevention of DCM at different stages are elaborated in one of our recent review articles (39).

Hyperglycemia leads to several changes in diabetic hearts. There is an increased production of reactive oxygen species (ROS) due to mitochondrial damage (45–47). The ROS contributes to cardiac fibrosis by instigating matrix metalloproteinases (MMPs), especially MMP-2 and −9 which are collagenases that degrade extracellular matrix (48–52). Cardiac fibrosis compromises cardiomyocyte contractility and cellular signaling leading to apoptosis. The remaining cardiomyocytes have more workload for contractility of the heart. As an adaptation, cardiomyocytes increase in size and hypertrophied. Hyperglycemia also increases the accumulation of inflammatory granules. Pro-inflammatory cytokines are increased in the diabetic heart and accumulate near hypertrophic cardiomyocytes (21). Increased fibrosis of extracellular matrix compromises the compliance of the heart that leads to diastolic dysfunction. Further, the left ventricular wall becomes thin and the geometric shape of the heart changes and left ventricle become more round-shape (21, 51) (Figure 1).

In DM hearts insulin signaling is compromised which causes altered metabolism, inflammation and apoptosis, mitochondrial damage and ROS generation, impaired calcium signaling, and cardiac hypertrophy and fibrosis (39, 41, 53). Several miRNAs are involved in the regulation of these changes in the DM heart, and differential expression of these miRNAs lead to pathological cardiac remodeling and cardiomyopathy (20, 27, 54, 55) (Figure 2).

3. MicroRNA

i) Background

MicroRNAs (miRNAs) are a novel class of non-coding RNA that modulate gene expression either by mRNA degradation or translational repression (10). They are an evolutionary conserved regulatory molecule which control almost all genes in biological processes. After

the discovery of the first miRNA Lin-4 in 1993, miRNA field has progressed enormously within a decade and miRNA is emerging as a potential therapeutic target for several diseases (56). There are more than two thousand miRNAs in humans (57), and each miRNA regulate more than one genes. Even one gene may be regulated by several miRNAs, which provides a layer of regulatory network for genes. Several members of the same family of miRNA may regulate a signaling cascade of a biological pathway or even one miRNA may regulate more than one genes in the same biological pathway (58). This complex regulatory network is not completely understood, however, there is consensus that miRNAs are a crucial regulator for a gene and/or several genes in a signaling pathway. In the human heart, there are nearly 18 miRNA families that contribute to nearly 90% of the total miRNAs present in the heart, and several dozens of them are differentially expressed in the failing heart (59). Overexpressing a downregulated miRNA or inhibiting an upregulated miRNA are novel approaches for mitigating cardiac remodeling and improving cardiac function in the diabetic heart.

ii) MiRNA biogenesis and function

MiRNA is transcribed as a primary miRNA (pri-miRNA) from intronic or intergenic region by RNA polymerase II/III as a single transcript or a polycistronic transcript (16). The pri-miRNA is approximately 200 nucleotides long with a hairpin loop and contains 5′ cap and 3′ poly A tail. The Pri-miRNA is processed by Drosha and DiGeorge syndrome critical region gene 8 (DGRC8) to form a precursor miRNA (pre-miRNA), which is approximately 70 nucleotides long double stranded structure. The pre-miRNA assembles in exportin5 and RanGTP to make a complex, which is exported into cytoplasm. In the cytoplasm pre-miRNA is processed by dicer, a RNase III endonuclease, into a mature miRNA which is immediately loaded into RNA induced silencing complex (RISC). The two strands of pre-miRNA may form one or two mature miRNAs depending on degradation of passenger strand of miRNA (miRNA* or miR-5p) (19, 60) (Figure 3).

Mature miRNA has a seed sequence which is 2–8 nucleotide from the 5′end. The seed sequence of miRNA if binds perfectly to the 3′untranslated region (UTR) of mRNA of a gene then it will degrade the mRNA but if the seed sequence match imperfectly with the 3′UTR of mRNA then it will block the translational machinery and impair protein synthesis (16, 19) (Figure 3).

iii) MiRNAs in cardiac regeneration

MiRNAs are documented to regulate cardiac stem cell differentiation, which is pivotal for cardiac regeneration (61–64). The extracellular matrix stiffness contributes to stem cell self-renewal (65), and survival and differentiation of cardiac stem cell (66, 67). MiR-1 and miR-133a promotes differentiation of embryonic stem cell into cardiac lineage by targeting histone deacetylase-4 and serum response factor, respectively (68). MiR-499 is also involved in regulation of embryonic stem cell into cardiomyocyte lineage (69).

MiRNAs also regulate stem cell homing, differentiation and maturation, which is crucial for cardiac regeneration (70, 71). Several recent reviews elaborate the potential roles of miRNA in cardiac regeneration (31, 72–78).

iv) MiRNAs in exosome improve cardiac functions of diabetic hearts

MiRNAs are released into circulation after encapsulation into a membrane-bound vesicle called exosome (31). These exosomes are also secreted from stem cell (79) and other cell types including cardiomyocytes (29), and plays a pivotal role in cardiac regeneration and regulation of cardiac functions (80–85). In diabetic heart, cardiomyocytes-derived exosomes have elevated levels of miR-320, which is detrimental to the heart (86). Therefore, exosome secretion inhibitor such as GW4869 could be a potential therapeutic strategy to mitigate exosome-mediated cardiac dysfunction in diabetic hearts (86–88).

4. MicroRNA as therapeutic target for diabetic cardiomyopathy

The expression of miRNA changes in the diabetic heart (21). It is not necessary that all miRNAs showing altered expression in diabetic heart may have a crucial role in diabetic cardiomyopathy, however, empirical evidences based on loss-, and gain-of function studies on miRNA revealed several miRNAs that regulate diabetic cardiomyopathy (89). For example, silencing of miR-195 (90) or upregulation of miR-30 (91) mitigates diabetic cardiomyopathy. MiR-141 is upregulated in diabetic hearts and it decreases ATP production by suppressing ATP synthase activity (92). Therefore, suppression of miR-141 can be a potential strategy to improve ATP production in the diabetic heart. MiR-133a is downregulated in the diabetic heart (21, 55, 93), and overexpression of miR-133a by a mimic reduces cardiac hypertrophy (55), fibrosis (94), and cardiac contractility (27). Therefore, targeting a particular miRNA involved in a specific signaling pathway in the diabetic heart may provide a therapeutic effect to ameliorate diabetic cardiomyopathy.

5. Conclusions

The two major types of diabetes, T1D and T2D, may have different pathophysiological adaptations due to different levels of insulin in the blood (95). The miRNA profiling in diabetic hearts revealed several crucial miRNAs that contribute to diabetic cardiomyopathy. These miRNAs can be either present in the heart or are released into an exosome. Empirical evidences demonstrate that modulating the expression of miRNA by either a mimic or an inhibitor has potential to ameliorate diabetic cardiomyopathy. Although these are encouraging results for developing miRNA-based therapeutic strategy for diabetic cardiomyopathy, further investigations are required to understand the regulatory mechanisms by which miRNAs cross-talk to optimize the gene expression in diabetic hearts, considering the fact that one miRNA may have more than one target and one gene can be targeted by more than one miRNA. From therapeutic point of view, it is also important to investigate how miRNA should be delivered and which route of delivery is better. Overall, there is consensus that miRNA is emerging as a therapeutic target for diabetic cardiomyopathy and future studies will determine its clinical application.

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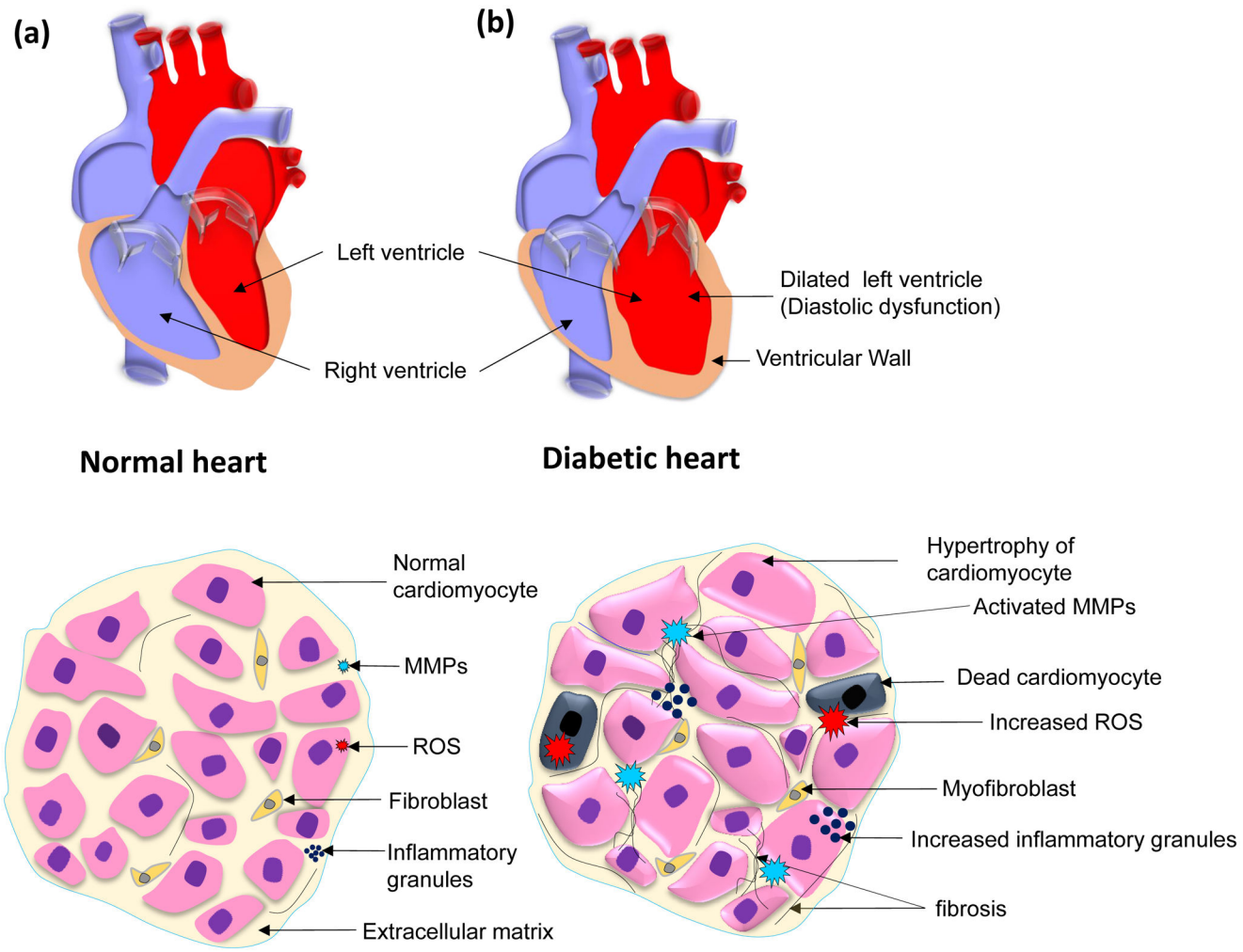

Figure 1.

Schematic representation for anatomical and histological features of diabetic cardiomyopathy. Top, schematic diagram showing a) a normal heart and, b) a diabetic heart. The dialated left ventricle is highlighted in the diabetic heart, which is a hallmark for diastolic dysfunction. Bottom, schematic diagram showing distinct histological featues of a a) normal and b) diabetic hearts, such as cardiomyocytes in diabetic heart shows hypertrophic cardiomyocytes, increased cardiomyocyte death, presence of myofibroblasts that respond to inflammation, increased interstitial and perivascular fibrosis, and ROS production, inflammation, and MMP activation.

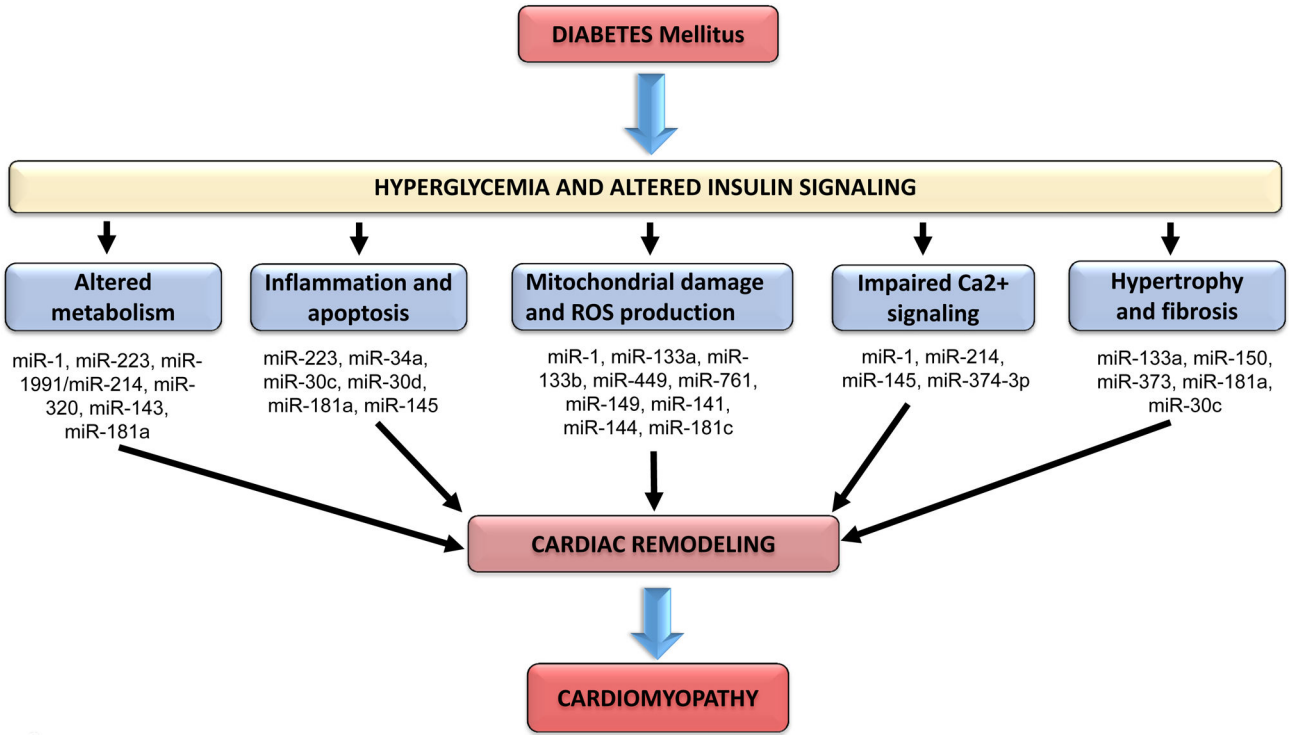

Figure 2.

Altered cellular pathways in diabetic hearts. MiRNAs associated with regulation of signaling genes in each pathways that lead to cardiac remodeling and diabetic cardiomyopathy.

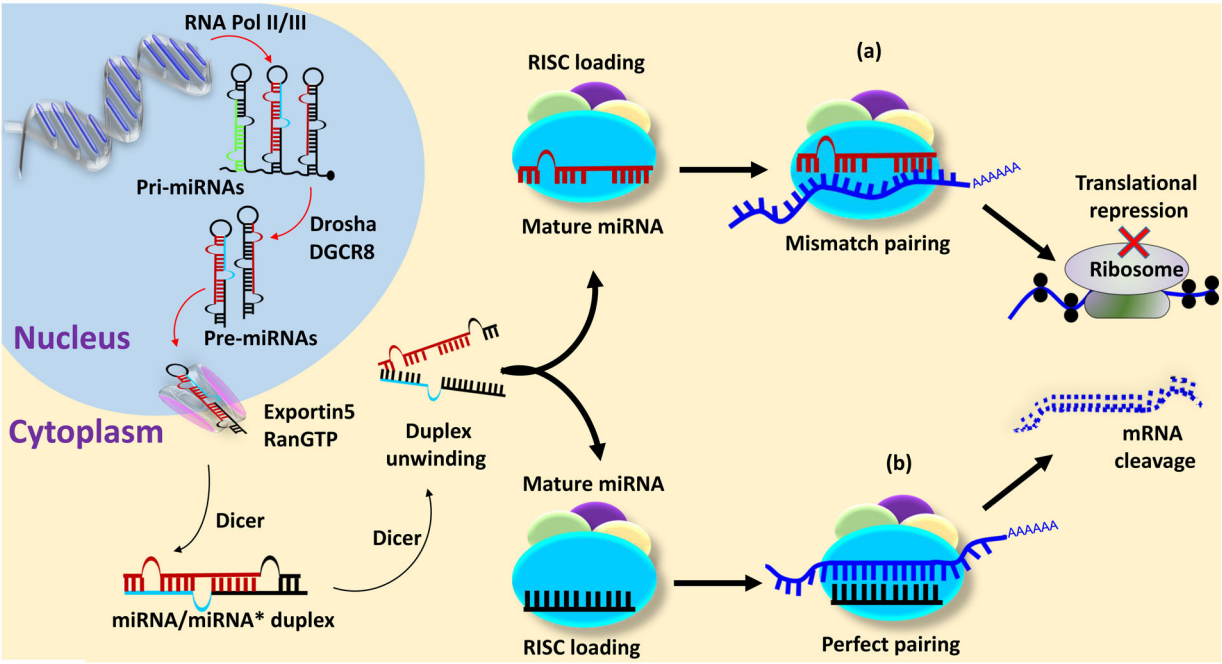

Figure 3.

MiRNA biogenesis and functions. Transcription of miRNA in the nucleus from non-coding DNA, their processing in the nucleus into primary miRNA (pri-miRNA) and precursor miRNA (pre-miRNA). Transport of pre-miRNA into cytoplasm and its processing by dicer into a mature miRNA, which is loaded into a RNA induced silencing complex (RISC). Mature miRNA can degrade mRNA when the seed sequence of miRNA perfectly match with the untranslated region of mRNA or inhibits translation of protein when the seed sequence imperfectly match with the untranslated region of mRNA.