MicroRNomics: a newly emerging approach for disease biology

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It is clear that gene expression in the human is precisely controlled in a cell, tissue, time, and condition-specific manner. Large-scale microarray data suggest that different cells, tissues, and organ systems within an organism (including humans) have different gene expression profiles, although they have the same genome. Moreover, these gene expression signatures are sensitive to changes in condition, such as development, diseases, environment changes, and therapeutic drugs (10, 36, 75, 94). Therefore, completely understanding the regulatory mechanisms of gene expression is one of the most important issues in genomic medicine. Surprisingly, recent analyses of the human and animal genomes have demonstrated that the majority of RNA transcripts are relatively small, noncoding RNAs (ncRNAs), rather than large, protein coding messenger RNAs (mRNAs). Moreover, these ncRNAs may represent a novel important layer of regulation for gene expression. The most important breakthrough in this new area is the discovery of microRNAs (miRNAs). miRNAs comprise a novel class of endogenous, small, noncoding RNAs that negatively regulate gene expression via degradation or translational inhibition of their target mRNAs. As a group, miRNAs may directly regulate ~30% of the genes in the human genome. In keeping with the nomenclature of RNomics, which is to study ncRNAs on the genomic scale, “microRNomics” is coined here to describe a novel subdiscipline of genomics that studies the identification, expression, biogenesis, structure, regulation of expression, targets, and biological functions of miRNAs on the genomic scale. A growing body of exciting evidence suggests that miRNAs are important regulators of cell differentiation, proliferation/growth, mobility, and apoptosis. These miRNAs therefore play important roles in development and physiology. Consequently, dysregulation of miRNA function may lead to human diseases such as cancer, cardiovascular disease, liver disease, immune dysfunction, and metabolic disorders. microRNomics may be a newly emerging approach for human disease biology.

miRNAs; genomics; gene expression; cancer; cardiovascular disease

Zhang C. MicroRNomics: a newly emerging approach for disease biology. Physiol Genomics 33: 139–147, 2008. First published February 26, 2008; doi:10.1152/physiolgenomics.00034.2008.—Genomic evidence reveals that gene expression in humans is precisely controlled in cellular, tissue-type, temporal, and condition-specific manners. Completely understanding the regulatory mechanisms of gene expression is therefore one of the most important issues in genomic medicine. Surprisingly, recent analyses of the human and animal genomes have demonstrated that the majority of RNA transcripts are relatively small, noncoding RNAs (ncRNAs), rather than large, protein coding messenger RNAs (mRNAs). Moreover, these ncRNAs may represent a novel important layer of regulation for gene expression. The most important breakthrough in this new area is the discovery of microRNAs (miRNAs). miRNAs comprise a novel class of endogenous, small, noncoding RNAs that negatively regulate gene expression via degradation or translational inhibition of their target mRNAs. As a group, miRNAs may directly regulate ~30% of the genes in the human genome. In keeping with the nomenclature of RNomics, which is to study ncRNAs on the genomic scale, “microRNomics” is coined here to describe a novel subdiscipline of genomics that studies the identification, expression, biogenesis, structure, regulation of expression, targets, and biological functions of miRNAs on the genomic scale. A growing body of exciting evidence suggests that miRNAs are important regulators of cell differentiation, proliferation/growth, mobility, and apoptosis. These miRNAs therefore play important roles in development and physiology. Consequently, dysregulation of miRNA function may lead to human diseases such as cancer, cardiovascular disease, liver disease, immune dysfunction, and metabolic disorders. microRNomics may be a newly emerging approach for human disease biology.

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MicroRNomics IN DISEASE BIOLOGY

Review

Gene Regulation

BIOGENESIS OF miRNAs AND THEIR ROLE IN GENE REGULATION

Mature miRNAs are noncoding, single-stranded RNAs of 18–24 nucleotides and constitute a novel class of gene regulators. miRNAs are initially transcribed by RNA polymerase II or III (Pol II or Pol III, respectively) in the nucleus to form large pri-miRNA transcripts, which are usually several kilobases long and are capped (MGpppG) and polyadenylated (14, 62). The pri-miRNAs are processed in the nucleus by the RNase III enzyme Drosha and the dsRNA binding protein Pasha (also known as DGC8), into ~70-nucleotide pre-miRNAs, which fold into stem-loop hairpin structures. RAN-GTP and exportin 5 transport the pre-miRNA into the cytoplasm. Subsequently, another RNase III enzyme, Dicer, processes the pre-miRNA to generate a transient ~18–24 nucleotide duplex. The duplex is loaded into the miRNA associated multiprotein RNA-induced silencing complex, which includes the Argonaute proteins. One strand of the miRNA is preferentially retained in this complex and becomes the mature miRNA; the opposite strand, known as the passenger strand or miRNA*, is eliminated from the complex. In addition to this pathway for miRNA biogenesis, some intronic miRNA precursors are able to bypass Drosha processing to produce miRNAs by Dicer, possibly representing an alternative novel pathway for miRNA biogenesis (61, 100).

The mature miRNA binds to complementary sites in the mRNA target to negatively regulate target gene expression in one of two ways. The mechanism of subsequent target gene suppression depends on the degree of complementarity between the miRNA and its target, in addition to other criteria that have yet to be defined. miRNAs that bind to mRNA targets with imperfect complementarity block target gene expression via translational silencing. In contrast, miRNAs that bind to their mRNA targets with perfect complementarity block target gene expression by translational silencing. However, the above opinion may not be completely correct. Recent studies suggest that even imperfect base-pairing of miRNA with its target mRNA can lead to a decreased abundance of the mRNA (5, 74).

MAJOR APPROACHES IN MicroRNomics

Microarray analysis of miRNAs on the genome scale is the most powerful method in microRNomics to determine the expression signature of cells, tissues, and organs within an organism under different conditions (7, 32, 107). Currently, there are 5,234 miRNAs that have been sequenced and added into the miRBase Sequence Database. Accordingly, microarray chips containing these updated miRNA probes for a specific organism are commercially available. For example, current human microarray probes include 711 miRNA probes.

Fig. 1. Biological function of microRNAs and their mechanisms.
human miRNAs, whereas 568 mouse miRNAs and 348 rat miRNAs are included in mouse microarray chips and rat microarray chips, respectively.

Computational approaches can be used in microRNomics to identify miRNAs and their target prediction (22, 44, 67, 119, 129). Computational methods to identify miRNA are based on the following three observations. First, miRNAs generally derive from precursor transcripts of 70–100 nucleotides with extended stem-loop structure. Second, miRNAs are usually highly conserved between the genomes of related species. Third, miRNAs display a characteristic pattern of evolutionary divergence. Lai has successfully identified Drosophila microRNAs using this computational approach (69). The more important application of the computational approach in microRNomics is to predict miRNAs’ mRNA targets. To bridge the bioinformatics void in the miRNA database with the in cyto and in vivo biology of an organism, a number of computer programs have been developed for prediction of mRNA targets (9, 45, 50, 80). The common criteria used for target prediction by these computer programs are as follows: 1) the degree of base complementarity between the miRNA and mRNA with special focus on identifying a perfect or near-perfect complementarity between a target mRNA and the miRNA in the “seed” region (i.e., nucleotides 2–8 of the miRNA); 2) the calculated thermodynamic stability of the predicted miRNA/mRNA complex; 3) the degree of conservation of orthologous target sites in the 3'-untranslated region (UTR) of different species.

The integrative analysis of miRNA expression with comparative genomics, transcriptomics, or proteomics is another important approach to study miRNA on the genome scale. Comparative genomics has been intensively used to discover a wide range of functional elements, including protein-coding genes, RNAs, and various classes of regulatory elements or motifs (83). Recent studies suggest that comparative genomics provides an opportunity to discover functional miRNAs systematically, making use of their conservation across multiple species (69, 94, 104). miRNAs is able to control a large-scale gene expression by directing their target mRNAs for degradation. Paired expression profiles of miRNAs and genome-wide miRNA expression (transcriptomic) approach is therefore a useful method to identify functional miRNA target relationship (49). Furthermore, the combination of miRNA research with proteome has been proven to be an important approach for miRNA study, because miRNAs control protein levels as their final step for the gene expression regulation (35, 113). This approach is particularly important because miRNAs control some protein expression by mRNA translational silencing, but not by mRNA degradation.

The data obtained from miRNA microarray and computational analyses should be verified experimentally by Northern blot and/or real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) (22, 24, 56). In addition, in situ hybridization is a good method to detect and localize miRNAs in both paraffin-embedded and frozen tissue sections (85, 103, 112). To verify the predicted target, a widely used method is to make a plasmid construct, which encodes a reporter, such as firefly luciferase, with a 3′-UTR containing the predicted miRNA target and transfect the reporter plasmid into a cell expressing the cognate mRNA. If the target and miRNA interact, a decrease in luciferase activity should be measured (1, 131). As a control, a similar reporter construct with a mutated target sequence is tested. The advantage of this method is that it is able to verify whether or not the miRNA is a direct target under this special condition in a cell. However, as one miRNA may have multiple mRNA targets, the tested mRNA needs to be verified as the major target in native experimental cells. Alternatively, one can inhibit the endogenous miRNA by introducing an antisense oligonucleotide to the cells and thus relieve miRNA-mediated repression of the target mRNA with increased expression as a result. Furthermore, an miRNA-targeted gene expression should be verified by qRT-PCR and Western blot at both mRNA and protein levels.

To verify the biological function of a specific miRNA, the following gain-of-function and loss-of-function approaches should be applied both in vitro in cultured cells and in vivo in mammals (56, 115). Virus-mediated miRNA gene transfer is the first choice for the gain-of-function experiments. In addition, transfer of its pre-mRNA into the cultured cells in vitro or tissues in vivo under some conditions is also suitable for the gain-of-function approach. For the loss-of-function experiments, antisense-based miRNA inhibitors or their modified forms are broadly used both in vitro and in vivo (56). However, efficacy is a big pitfall for these inhibitors in vivo. Thus, miRNA knockout mice, especially conditional knockout mice, should be the most powerful loss-of-function approach.

**CELLULAR FUNCTIONS of miRNAs**

miRNAs regulate the expression of over 10,000 genes in a cell. It is therefore not surprising that miRNAs are involved in the regulation of almost all major cellular functions, such as cell differentiation, proliferation/growth, mobility, and apoptosis (Fig. 1). These cellular effects of miRNAs are demonstrated in many different cells, such as cancer cells and cardiovascular cells (4, 34, 53, 58, 96). Thus, we have summarized these cellular effects here using cardiovascular cells as examples.

The role of miR-1 in cardiomyocyte differentiation was discovered in 2005 (130). It was found that the miR-1 gene is a direct transcriptional target of several muscle differentiation regulators, including serum response factors, myogenic differentiation factor D, and the myocyte enhancing factor 2 (130). Correspondingly, excess miR-1 in the developing heart leads to a decreased pool of proliferating ventricular cardiomyocytes, suggesting that miR-1 genes modulate the effects of critical cardiac regulatory proteins to control the balance between differentiation and proliferation during cardiogenesis.

The role of miRNAs in cardiac myocyte growth has been documented in three recent studies (24, 101, 115). Overexpression of miR-23a, miR-23b, miR-24, miR-195, or miR-214 via adenovirus-mediated gene transfer induced hypertrophic growth of cultured cardiomyocytes, whereas overexpression of miR-150 or miR-181b caused a reduction in cardiomyocyte cell size (115). We have recently shown that miRNAs are aberrantly expressed in cultured neonatal hypertrophic cardiomyocytes that are stimulated by angiotensin II or phenylephrine (24). Modulating an aberrantly upregulated miRNA such as miR-21, via antisense-mediated knockdown, has a significant negative effect on cardiomyocyte hypertrophy in vitro (24). In contrast, overexpression of an aberrantly downregulated miRNA such as miR-1, via adenovirus-mediated gene
miR-15a and miR-16-1 downregulation in chronic lymphocytic leukemia
downregulation in a wide range of tumors such as breast, colon, lung, prostate, and pancreatic endocrine
dowregulation in lung and colon cancers
dowregulation in breast cancer
upregulation in many tumors such as breast cancer and glioblastomas
upregulation in heart with hypertrophy and vessel with neointimal formation
dowregulation in colorectal cancer, breast cancer and B-cell malignancies
upregulation in heart with hypertrophy
upregulation in heart with hypertrophy
upregulation in heart with hypertrophy
upregulation in heart with hypertension
upregulation in ischemic heart tissue
upregulation in diabetic heart

tumor suppressor
tumor suppressor
tumor suppressor
tumor suppressor
induces cardiac hypertrophy and neointimal lesion formation
induces cardiac hypertrophy
induces cardiac hypertrophy
inhibits cardiac hypertrophy
inhibits cardiac hypertrophy

BcL-2
E2F1, Tsp1, CTGF
Ras, PRDM1
MYC (?)
ERBB2, ERBB3
PTEN, Bcl-2 (?), PDCD4
PTEN, Bcl-2 (?), PDCD4

miR, micro-RNA.
to mediate their effects largely by downregulating the anti-apoptotic protein, BCL-2. This protein is often expressed at very high levels in CLL and is thought to be important for the survival of the malignant cells. Thus, the decreased expression of miR-15a and miR-16-1 results in the elevated levels of BCL-2 (17, 18, 27). Moreover, expression of these miRNAs is capable of inducing apoptosis in leukemia cell lines. The evidence suggests miR-15a and miR-16-1 may be important targets for CCL treatment.

The second group of miRNAs that are well documented in cancer is the miR-17-92 cluster that is frequently upregulated in lymphomas. This cluster consists of the seven following individual miRNAs: miR-17-5p, 17-3p, 18, 19a, 19b1, 20, and 92. All of these miRs are encoded from a frequently amplified locus at 13q31.3 (47, 88). It was shown that the miR-17-92 cluster, but not the individual miRNAs, can enhance tumorigenesis by inhibiting apoptosis in tumors (47). Further studies in human cell lines showed that transcription of the miR-17-92 cluster was directly regulated by c-Myc and that the individual miRs-17-5p and miR-20 regulate the translation of E2F1, a transcription factor with both proapoptotic and proproliferative activity (48). Thus, coexpression of c-Myc and miR-17 is believed to fine tune E2F1 activity so that proliferation is enhanced and apoptosis is inhibited (87). In addition to its confirmed role in lymphoma development, this miRNA cluster may also have broad significance in tumor biology, as members of this cluster are overexpressed in a wide range of tumors such as breast, colon, lung, prostate, and pancreatic endocrine (46).

Another group of cancer-related miRNAs that are extensively studied are miR-155 (37, 63, 64), the let-7 family (57), miR-125a and miR-125b (102), miR-21 (21), miR-143, and miR-145 (2). miR-155 is overexpressed in many tumors including B-cell lymphomas, Burkitt lymphoma, Hodgkin’s lymphoma, and breast, lung, colon, and thyroid cancers. Although the molecular mechanisms involved in miR-155-mediated procarcinogenesis are not clear, the interaction between miR-155 and the oncogene MYC seems to be one of the mechanisms. Intriguingly, mice overexpressing miR-155 under control of the Eμ enhancer are able to develop B-cell malignancy rapidly (28). Let-7 family members of miRNAs are also downregulated in lung and colon cancer cells. It was observed that low Let-7 expression correlated with a shortened postoperative survival in lung cancer patients who had undergone potentially curative operative procedures. miR-125a and miR-125b, whose expression is frequently lost or reduced in breast cancer, have been reported to regulate the important oncogenes ERBB2 and ERBB3. miR-21 is found to be overexpressed in many human tumors, such as breast cancers and glioblastomas, and has been confirmed as an oncomiRNA via its antitumor effect. miR-143 and miR-145 are often downregulated in colorectal and breast cancers as well as B-cell malignancies, and there may be cancer related miRNAs in other human cancers.

MicroRNomics IN CARDIOVASCULAR DISEASE

Cardiac hypertrophy is a common pathological response to a number of cardiovascular diseases such as hypertension, ischemic heart disease, valvular diseases, and endocrine disorders. Cardiac hypertrophy often leads to heart failure in humans and is a major determinant of mortality and morbidity in cardiovascular diseases. miRNAs are important regulators for the differentiation and growth of cardiac cells, and it is therefore reasonable to hypothesize that miRNAs play important roles in cardiac hypertrophy and heart failure.

Almost simultaneously, three independent groups (including the current author) reported dramatic results in the miRNA expression signature of mouse hearts that were made hypertrophic by either aortic binding or expression of activated calcineurin (24, 101, 115) (Table 1). It should be noted that miRNAs are aberrantly expressed in hypertrophic hearts in both animal models, and these results were confirmed by in vitro studies of cardiac myocytes with hypertrophy (24, 101, 111, 115). Furthermore, overexpression of some miRNAs that are upregulated in hypertrophic hearts induces cardiac myocyte hypertrophy, whereas overexpression of some miRNAs that are downregulated in hypertrophic hearts prevents cardiac myocyte hypertrophy. On the other hand, inhibition of miR-21, an miRNA that is upregulated in the hypertrophic animal and human hearts, inhibits hypertrophic hearts in vitro (24). The role of miR-21 was further confirmed by another group (111).

In vivo, overexpression of miR-195, a miRNA that is upregulated in hypertrophic hearts, is sufficient to induce cardiac hypertrophy (115), while a gene mutation or “decoy” approach has confirmed the role of miR-208 and miR-133 in cardiomyocyte hypertrophy (20, 114). Taken together, these findings demonstrate that multiple miRNAs are involved in cardiac hypertrophy and that modulating one aberrantly expressed miRNA is sufficient to modulate the hypertrophy. However, the molecular mechanisms responsible for individual miRNA-mediated effects on cardiac hypertrophy are unclear.

More recently, the roles of miRNAs in human cardiac hypertrophy and heart failure have been elucidated in several clinical studies (76, 115, 126). Northern blot analysis of the hypertrophy-regulated miRNAs in idiopathic, end-stage, failing human hearts shows that the expression of miR-24, miR-125b, miR-195, miR-199a, and miR-214 is significantly increased compared with control hearts (115). Forty-three out of 87 detected miRNAs are aberrantly expressed in hearts with ischemic cardiomyopathy, dilated cardiomyopathy, or aortic stenosis (87), indicating that miRNAs are indeed involved in the pathophysiology of human cardiac hypertrophy and heart failure.

Neointimal lesion formation is a common pathological lesion found in diverse cardiovascular diseases such as atherosclerosis, coronary heart diseases, postangioplasty restenosis, and transplantation arteriopathy. Using microarray analysis and a well-established neointimal formation model, we determined the miRNA expression profile in the vascular wall with neointimal lesion formation (24). Compared with normal, uninjured arteries, microarray analysis demonstrated that aberrant miRNA expression is a characteristic of vascular walls after angioplasty. Those miRNAs that are highly expressed in the rat carotid artery and are more than onefold upregulated or 50% downregulated after angioplasty were further verified by qRT-PCR and/or Northern blot analysis (24). Modulating an aberrantly overexpressed miRNA, miR-21, via antisense-mediated knockdown has a significantly negative effect on neointimal lesion formation in rat artery after angioplasty (Fig. 2). These results indicate that miRNAs are important regulators in the development of proliferative vascular diseases (Table 1).

Cardiac arrhythmias in the setting of ischemic heart disease remain a serious health problem because of their sudden and
unpredictable nature and their potentially grave consequences. In a rat model of myocardial infarction and in human heart with coronary heart disease, the muscle-specific miRNA, miR-1, was significantly upregulated in ischemic heart tissue (126). To further determine the role of miR-1 in arrhythmogenesis, both gain-of-function and loss-of-function approaches were applied to enhance or inhibit miR-1 expression in the infarcted myocardium. The results show that injection of mature miR-1 exacerbates arrhythmogenesis, whereas elimination of miR-1 by an antisense inhibitor suppresses arrhythmias. The results indicate that miR-1 has proarrhythmic, as well as arrhythmogenic effects (126). Silencing the genes for the ion channels GJA1 and KCNJ2 verified that these proteins are important players in the miR-1-mediated arrhythmogenic effect (126) (Table 1).

miR-133 expression is upregulated (123) in diabetic rabbit heart. The ether-a-go-go-related gene (ERG), a long QT syndrome gene encoding a key K+ channel (IKr) in cardiac cells, was confirmed to be a target for miR-133 (123). Delivery of exogenous miR-133 into the rabbit myocytes and cell lines produces posttranscriptional repression of ERG, thereby downregulating ERG protein levels without altering its transcript level, subsequently causing substantial depression of IKr, an effect that is abrogated by the miR-133 antisense inhibitor (123). Thus, depression of IKr via repression of ERG by miR-133 may contribute to the slowing of myocyte repolarization and, thereby, QT prolongation and the associated arrhythmias in diabetic hearts (Table 1).

In cardiac cells, KCNQ1 assembles with KCNE1 and forms a channel complex constituting the slow delayed rectifier current Ik,β in cardiac cells, was confirmed to be a target for miR-133 (123). Delivery of exogenous miR-133 into the rabbit myocytes and cell lines produces posttranscriptional repression of ERG, thereby downregulating ERG protein levels without altering its transcript level, subsequently causing substantial depression of Ik,β, an effect that is abrogated by the miR-133 antisense inhibitor (123). Thus, depression of Ik,β via repression of ERG by miR-133 may contribute to the slowing of myocyte repolarization and, thereby, QT prolongation and the associated arrhythmias in diabetic hearts (Table 1).

As mentioned earlier, although miRNA expression profiles in some humans have been determined recently, the probe content of these miRNA microarray chips only contain parts of the entire human miRNA repertoire. As all the 1,000 human miRNAs are eventually identified and sequenced, using miRNA microarray chips containing all the human miRNAs for expression signatures in diverse human diseases will be critical to identify the key miRNAs responsible for a particular disease state. We predict that more and more disease expression profiles of miRNAs will be presented in the next several years. As all the 1,000 human miRNAs are eventually identified and sequenced, using miRNA microarray chips containing all the human miRNAs for expression signatures in diverse human diseases will be critical to identify the key miRNAs responsible for a particular disease state. We predict that more and more disease expression profiles of miRNAs will be presented in the next several years.

miRNAs are also involved in the regulation of insulin release and cholesterol metabolism. Dysfunction of these miRNAs might be related to some metabolic disorders. For example, miR-375 was shown to directly regulate insulin secretion from pancreatic islet cells (93). Upregulation of miR-375 led to an enhanced inhibition of insulin release. In contrast, the miR-375 inhibitor enhanced insulin secretion via blocking the effect of the miRNA (93). miR-122 is an important miRNA in liver. Antisense targeting this miRNA revealed that inhibition of miR-122 resulted in decreased levels of cholesterol in the plasma and improved liver function in obese mice (39). Recent studies demonstrated that some miRNAs such as miR-155 (98, 117), miR-146, and miR-181a were able to regulate T and B cell function (73, 110). Thus, miRNAs are also implicated in immune function regulation, and dysregulation of these miRNAs may be related to some immune and inflammatory disorders (84, 86, 109).

CLOSING REMARKS AND PERSPECTIVE

Investigating the role of miRNAs in disease biology is a new frontier in biomedical research. Although the newly coined term microRNomics has increasingly been used in personal communications to describe this new subdiscipline of genomics, there is no formal nomenclature reported previous to this review article. While the field of miRNAs is at an early stage, the study of their roles in human disease has a history of less than 3 yr; increasing evidence has revealed that miRNAs may play important roles in human disease development, progression, prognosis, diagnosis, and evaluation of treatment response. Moreover, miRNAs may represent a novel new therapeutic target in diverse human diseases.

As mentioned earlier, although miRNA expression profiles in some humans have been determined recently, the probe content of these miRNA microarray chips only contain parts of the entire human miRNA repertoire. As all the 1,000 human miRNAs are eventually identified and sequenced, using miRNA microarray chips containing all the human miRNAs for expression signatures in diverse human diseases will be critical to identify the key miRNAs responsible for a particular disease state. We predict that more and more disease expression profiles of miRNAs will be presented in the next several years. Based on these novel microRNomics data, the key miRNAs for a specific disease and their mRNA targets will be further verified by experimental approaches.

An important avenue for future research is the development of therapies based on miRNAs. A promising approach is to
target disease-related miRNAs using anti-miRNA oligos (miRNA inhibitors) to knock down overexpressed miRNAs or their mature or precursor form, to increase downregulated miRNAs. In animals and cultured cells, these oligos are proving to have promising therapeutic effects. However, until now, no studies in humans have been performed in vivo. One challenge of these treatments is the delivery method to transfer the miRNAs into the desired tissues. Given that these oligos cannot discriminate between healthy and diseased cells, side effects of these treatments remain a concern. Nevertheless, with a deeper understanding of the pharmacology of these oligos, the molecular mechanisms of miRNA actions, and the development of new delivery technologies, these small molecules may well fulfill their promise as valuable novel therapeutics.

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REFERENCES


MicroRNomics IN DISEASE BIOLOGY


