The potential function of microRNAs as biomarkers and therapeutic targets in multiple myeloma (Review)

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Abstract. Multiple myeloma (MM), accounting for ~1% of all types of human cancer and 13% of all hematological malignancies, is characterized by the malignant proliferation of monoclonal plasma cells (PCs) in the bone marrow. MM leads to end stage organ impairment, including bone lesions, renal dysfunction, hypercalcemia and anemia. So far, the specific pathogenesis of MM remains unclear and no early-stage sensitive biomarker of MM has been well characterized. Furthermore, treating MM is difficult, as the majority of patients eventually relapse or become refractory following treatment using presently available methods. To date, a number of studies have demonstrated that microRNAs (miRNAs) may serve crucial functions in the progression of numerous cancers, including MM. During the tumorigenesis and pathogenesis of MM, there are multiple carcinogenic events that involve the pernicious transformation from normal to malignant PCs. miRNAs, as oncogenes or tumor suppressors, regulate MM progression-related signaling pathways. In the present review, the up-to-date preliminary basic studies and associated clinical works on the underlying mechanisms of aberrant miRNA profiling in MM have been summarized, including an evaluation of its value as a potential biomarker and a novel therapeutic strategy for MM.

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1. Introduction

Multiple myeloma (MM) is the second most common cause of hematological malignancy-associated mortality in America, second only to non Hodgkin's lymphoma (1). The incidence of MM in Asia is 0.5-1/100,000, whereas the incidence in Africa and America is 10-12/100,000 (2). Generally, the median age of patients diagnosed with MM is 69 years old, and two thirds of patients are male (3). Over the previous two decades, the median survival time of patients with MM has increased from 3 to 6 years due to improvements in available treatments (4). However, the majority of patients have only a several-year remission and will eventually relapse or become refractory, with MM accompanied by severe multiple systemic lesions (5,6).

The pathogenesis of MM includes multistep carcinogenic events. Monoclonal gammopathy of undetermined significance (MGUS), the pre-malignant condition of MM, is typically followed by smoldering myeloma and finally develops into MM (7). A previous report indicated that patients with MGUS progress to MM or other associated malignant tumors at a rate of 1% per year (8). Therefore, it is important to accurately classify the different stages of MM to identify early stage and high-risk patients to enable timely clinical intervention (9).

At present, the treatment for MM includes autologous stem cell transplantation (ASCT) and the combined application of multiple chemotherapeutic drugs (10,11). However, there are a number of limitations with present therapeutic strategies. Firstly, patients with MM have differing responses to the same standardized treatment and drug-resistance may be induced. Secondly, although disease-free survival has been prolonged in patients with MM, the majority relapse eventually and the condition is more complicated following relapse (12). Therefore, uncovering more effective biomarkers and therapeutic agents for MM is desirable (13-15).

MicroRNAs (miRNA/miRs) are small (~22 nucleotides) non-coding RNAs that are associated with the initiation and progression of tumors by regulating ~30% genes at a post-transcriptional level (16). Accumulating evidence has demonstrated that miRNAs may be associated with regulating cellular apoptosis, proliferation, differentiation, metabolism, invasion and migration *in vitro* (17-19). The regulatory mechanisms of miRNAs in tumor cells have been studied extensively and the majority of the results concur that mature miRNAs are loaded into the RNA-induced silencing complex, which

results in the degradation or translational inhibition of their targets depending on perfect or partial base complementarity with the 3' untranslated region (UTR) of genes (20,21). This mode of interaction between miRNAs and their target genes in tumor cells means that they possess the potential to become novel therapeutic agents via the knockdown onco-miRs or the restoration of tumor-suppressive (TS)-miRs (22). Additionally, aberrant miRNA expression profiling in MM may be used as a biomarker for tumor classification, grading and clinical outcomes prediction in addition to providing the rationale for clinical individual therapy (7,23).

2. miRNAs deregulated in MM

MM is a heterogeneous malignancy with complex genetic abnormalities, including the presence of hypodiploidy, gene mutations, chromosome translocations, amplifications and deletions (24). Emerging evidence demonstrates that the expression of miRNA may be affected by numerous genetic diversities, including genomic alterations (25), transcriptional regulation (26), epigenetic regulation (27,28), RNA editing and sequence variations in miRNA binding sites, including in SNPs (29).

Dysregulated miRNAs in MM often serve similar functions in pathological processes as oncogenes or tumor suppressor genes via the activation of multiple signaling pathways associated with MM, including the nuclear factor-κB (NF-κB) signaling pathway (30), interleukin (IL)6/signal transducer and activator of transcription (STAT)3 signaling pathway (31), tumor protein P53 (P53)/mouse double minute 2 homolog signaling pathway (32) and phosphatidylinositide 3-kinases (PI3K)/protein kinase B (AKT) signaling pathway (33). During the occurrence and development of MM, the regulatory mechanisms of these miRNAs also provide the theoretical foundation for clinical-associated application research in the future (Fig. 1).

miRNA expression profiling analyses in MM. Increasingly, evidence suggests that aberrant miRNA expression is a hallmark in patients with MM, and that normal PCs have distinct miRNA expression profiles with malignant PCs. Zhou *et al* (34) profiled the miRNA expression pattern of syndecan-1 (CD138)⁺ cells isolated from 52 newly diagnosed patients with MM and two healthy donors (HDs), and revealed an elevated total miRNA level in malignant PCs. Microarray data analyses demonstrated that 39 miRNAs including miR-18, miR-92a, miR-181a, miR-181b, miR-221 and miR-222 were consistently expressed at higher levels in samples from newly diagnosed cases compared with HDs, whereas only miR-370 was downregulated in MM.

Although MM is a type of cancer that originates from malignant PCs in bone marrow, it also exerts considerable influence on ectopic miRNA expression profiles in body fluid, including serum, plasma, urine etc. Hao *et al* (35) performed a miRNA expression profile analysis on the serum samples from seven newly diagnosed symptomatic patients with MM and five HDs using the miRCURY™ LNA Array, and the results indicated that amongst all 1,891 miRNAs, 4 miRNAs were upregulated and 23 were downregulated. miR-214 (fold change of 4.80), miR-135b (fold change of 3.60), miR-132 (fold change of 0.43) and miR-92a (fold change of 0.49) among them were selected to be further validated in a large cohort of 108 newly diagnosed

patients with MM and 44 HDs by RT-qPCR assay due to their critical function in regulating the differentiation of osteoclasts and osteoblasts as previously reported. Results confirmed that the level of miR-214 (2.34 vs. 0.23, P=0.0005) and miR-135b (1.83 vs. -0.18, P=0.0022) were significantly increased in patients with MM compared with HDs. Furthermore, the receiver operating characteristic (ROC) analysis revealed that miR-214 and miR-135b may offer a powerful diagnostic tool for the identification of bone disease related to MM with high sensitivity and specificity.

In general, these previous studies disclosed a series of abnormally expressing miRNAs in patients with MM compared with HDs by high-throughput screening technologies, summarized in Table I (10,35-43). However, the results from these studies do not appear to be consistent. This discrepancy may partly be due to the differences in the platforms used for microarray technologies, the number of miRNAs analyzed, and the types and sizes of the samples included and the statistical methods designed.

In addition to being associated with clinical pathological parameters, a number of these deregulated miRNAs may be involved in the pathogenesis of MM. Global abnormal miRNA expression profiling provide the basis for further investigations on the specific functions of a single miRNA in the pathogenesis of MM. Firstly, further *in vitro* and *in vivo* experiments on the function of miRNAs are required to validate their biological function in MM. Subsequently, it is important to determine the potential mRNA targets of the deregulated miRNAs and investigate the underlying mechanism. In previous years, numerous bioinformatic softwares using different computational algorithms have been well developed to predict miRNA targets including TargetScan (http://www.targetscan.org) (44), miRanda (http://www.microRNA.org) (45) and PicTar (http://pictar.mdc-berlin.de/) (46). A number of studies selected the intersection of a number of different software predicted target genes in order to conduct in-depth research. This putative binding relationship should be validated using dual-luciferase reporter assays, the change of luciferase activity will decide whether this miRNA may bind directly to the the 3'UTR of its target gene (47).

Functional studies of dysregulated miRNAs in MM. Following the identification of dysregulated miRNAs in MM, an increasing number of studies have emphasized how these small molecules function in the process of transformation from normal PCs to malignant PCs. These studies demonstrate that miRNAs may exert an important function in regulating cell processes (including apoptosis, proliferation, migration and the cell cycle) in MM by directly binding to the corresponding target genes. Table II (18,36,48-55) and Table III (18,27,33,38,56-71) summarize all deregulated miRNAs and their target genes in MM. The understanding of this mode of interaction in MM will lay the theoretical foundation for the clinical miRNA-based therapy.

miR-17-92 cluster. miR-17-92 cluster, located in chromosome 13q31.3, including miR-18a, miR-20a, miR-92, miR-17 and miR-19a/b, is activated by the oncogene MYC proto-oncogene, BHLH transcription factor (C-MYC) and its expression is upregulated in a variety of types of cancer (72). It has previously been verified that an abnormally elevated expression of the miR-17-92 cluster is involved in the malignant progression of MM (52,73). Pichiorri *et al* (36) reported that the miR-17-92 cluster was
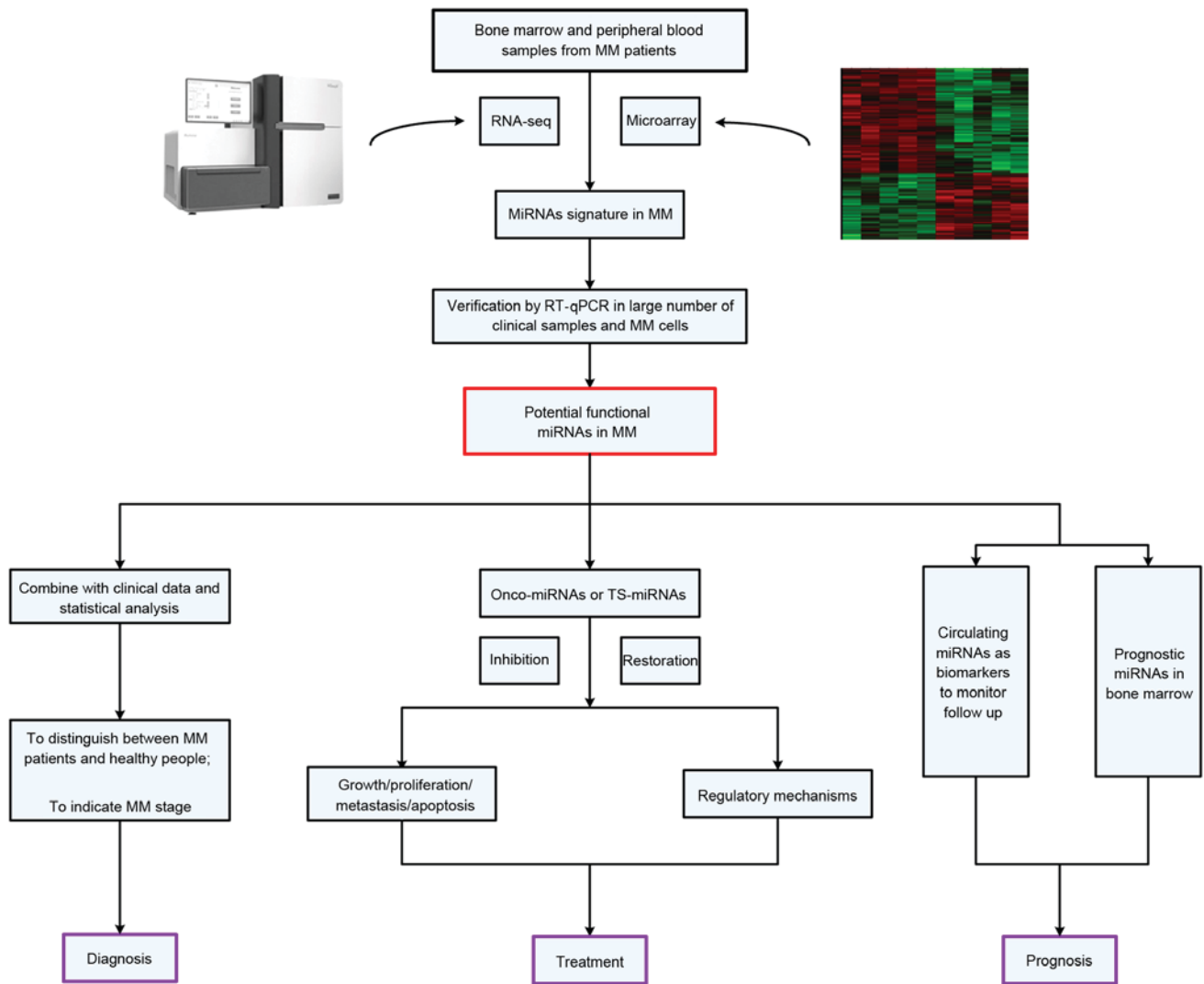
Figure 1. The sourcing, verification and potential applications of miRNAs in clinical-associated application research for MM. MM, multiple myeloma; miRNA, microRNA; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; TS-miRNA, tumor-suppressive miRNA.

significantly increased in the malignant PCs of patients with MM compared with normal ones of HDs. Additionally, the cluster members miR-19a and miR-19b were able to downregulate the protein expression of suppressor of cytokine signaling 1 (SOCS1), and then promote the proliferation of MM cells. It is well acknowledged that SOCS1 is a negative regulator of the signaling pathways mediated by IL6, and the precise mechanism is partially due to the fact that its decreased expression may induce the phosphorylation of signal transducer and activator of transcription 3 (STAT3), eventually resulting in unlimited growth of tumor cells (31,74). Furthermore, it has been revealed that miR-19 targeted the BCL2 like 11 gene and downregulated its protein expression, resulting in reduced apoptosis and the increased proliferation of malignant PCs. Although this cluster has a recognized carcinogenic effect in tumors, studies have also revealed that it may function as a tumor suppressor gene in inhibiting the proliferation in breast cancer cells. Additionally, Gutierrez *et al* (75) reported that the expression of miR-20a, miR-18a and miR-19b were downregulated in patients with MM with retinoblastoma gene deletion. It was suggested that this cluster may serve a different function in different subtypes of MM. It is worth mentioning that no abnormal expression

of the miR-17-92 cluster is present in MGUS, indicating that the miR-17-92 cluster may participate in the progression from MGUS to MM and has the potential to be used to distinguish MGUS from MM.

miR-29 family. The miR-29 family includes miR-29a, miR-29b and miR-29c, have been reported to possess a significant tumor inhibitory effect and are downregulated in hematological malignancies via regulating cell proliferation, differentiation and apoptosis (76,77). Amongst a variety of miRNAs, the miR-29 family represents a prototypical example of epi-miRNAs by targeting epigenetic regulators including DNA methyltransferases (DNMTs). In MM, miR-29b was revealed to target DNMTs, resulting in the demethylation of SOCS1 and an increase of its protein expression. SOCS1 inhibited the phosphorylation of its receptor, then inhibited the activation of STAT3 by binding with Janus Kinase, which finally resulted in the decreased proliferation of MM cells via the suppression of the transcription of downstream genes (61). In addition, miR-29b may also negatively regulate the PI3K/AKT signaling pathway. miR-29b inhibited the phosphorylation of AKT and re-activated suppressed apoptosis-promoting proteins, including P53, BCL2

Table I. High throughput screening of miRNAs with abnormal expression in MM.

Type of sample	Sample size	Platform	Dysregulated miRs in MM validated by RT-qPCR	Refs.
CD138+ PCs, MM cell lines	41 MM cell lines, 10 untreated MM, 4 N	Academic miRNA microarray	Up: miR-32, miR-17-5, miR-19a, miR-19b, miR-20a, miR-92, miR-106a, miR-106b, miR-93, miR-25, miR-181a/181b	(36)
CD138+ PCs, MM cell lines	7 MM cell lines, 10 untreated MM, 2 N	miRCURY™ LNA microarray	Up: miR-365, miR-193	(37)
CD138+ PCs	15 relapsed/refractory MM, 4 N	Liquid phase Luminex microbead miRNA profiling	Up: miR-181a/181b, miR-382, miR-222, miR-221 Down: miR-15a, miR-16	(38)
CD138+ PCs	52 untreated MM, 2 N	Agilent miRNA microarray V2	Up: miR-15b, miR-16, miR-19b, miR-21, miR-22, miR-29c, let-7a, let-7d, let-7f	(10)
CD138+ PCs	33 untreated MM, 5 MGUS, 9 N	μRNA microarray	Up: miR-21, miR-16, miR-221, miR-200b, miR-19a, miR-342; Down: miR-15a	(39)
Serum	14 untreated MM, 21 follow-up MM, 7 N	Agilent miRNA 15K array	Up: let-7b, miR-106a Down: miR-98, miR-16, let-7c, let-7i	(40)
Peripheral mononuclear cells	5 untreated MM, 5 N	Applied Biosystems miProfile miRNA qPCR arrays	Up: miR-16-1, miR-21, miR-24-1, miR-28, miR-33a, miR-101-1, miR-124-1, miR-125a, miR-125b-1, miR-129-1, miR-139, miR-145, miR-149, miR-202, miR-212, miR-221, miR-410, miR-424, miR-1297 Down: miR-23a, miR-520e	(41)
Extracellular supernatant fluid of BM	20 relapsed/refractory MM, 8 N	Agilent miRNA microarray v3	Down: let-7a, let-7b, miR-15a, miR-16, miR-20a, miR-106b, miR-223	(42)
Serum	7 untreated MM, 5 N	miRCURY™ LNA microarray	Up: miR-214-3p, miR-135b-5p, miR-4254, miR-3658 miR-33b; Down: miR-19a, miR-92a	(43)
Serum	7 untreated MM, 5 N	miRCURY™ LNA microarray	Up: miR-214, miR-135b, miR-132; Down: miR-92a	(35)

miR/miRNA, microRNA; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; N, normal controls; BM, bone marrow; Up, upregulated; Down, downregulated; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; CD138, syndecan 1; PC, plasma cells; Refs., references.

Table II. Principal oncogenic microRNAs with upregulation in MM.

MicroRNAs	Cell processes	Validated target genes	Refs.
miR-221/222	Cell apoptosis, cell proliferation	p27Kip1, p57Kip2, PUMA, PTEN	(48-50)
miR-17-92 cluster	Cell apoptosis, cell proliferation	BIM, SOCS1, IL-17RA, IL-17RE, IL-17RC	(18,36,51,52)
miR-181a/b	Cell apoptosis, cell proliferation	PCAF	(36,53)
miR-106b-25 cluster	Cell apoptosis, cell proliferation	PCAF	(36)
miR-32	Cell apoptosis, cell proliferation	PCAF	(36)
miR-135b	Cell differentiation	SMAD5	(54)
miR-125a	Cell apoptosis, cell proliferation	P53	(36)
miR-301a	Cell apoptosis, cell proliferation	TIMP2	(55)

miR, microRNA; MM, multiple myeloma; p27Kip1, cyclin dependent kinase inhibitor 1B; p57Kip2, cyclin-dependent kinase inhibitor 1C; PUMA, BCL2 binding component 3; PTEN, phosphatase and tens in homolog; BIM, BCL2 like 11; SOCS1, suppressor of cytokine signaling 1; IL-17, interleukin-17; PCAF, p-300-CBP associated factor; SMAD5, SMAD family member 5; P53, tumor protein p53; TIMP2, TIMP metallopeptidase inhibitor 2; Refs., references.

Table III. Principal tumor suppressor microRNAs downregulated in MM.

MicroRNAs	Cell processes	Validated target genes	Refs.
miR-125b	Cell apoptosis, cell proliferation	IRF4	(56)
Let-7b	Cell apoptosis, cell proliferation	IGF-1R	(57)
miR-29 family	Cell apoptosis, cell proliferation, cell migration	DNMT3A, DNMT3B, PSME4, Sp1, CDK6, MCL-1	(58-62)
miR-34a	Cell apoptosis, cell proliferation	NOTCH1, BCL2, CDK6	(63-65)
miR-202	Cell apoptosis, cell proliferation	BAFF	(33,66)
miR-15a/16	Cell apoptosis, cell proliferation, cell migration, cell cycle, angiogenesis	FGFR1, PIK3α, PI3KC2A, MDM4, VEGF	(38,67,68)
miR-214	Cell apoptosis, cell proliferation, cell cycle	PSMD10, ASF1B	(27)
miR-192, 194, 215	Cell apoptosis, cell proliferation, cell cycle	MDM2, IL-17R	(18)
miR-33b	Cell apoptosis, cell proliferation, cell migration	PIM-1	(69)
miR-126	Cell proliferation	C-MYC	(70)
miR-130b	Cell apoptosis, cell proliferation	GR-α	(71)

miR, microRNA; MM, multiple myeloma; IRF4, interferon regulatory factor 4; IGF-1R, insulin-like growth factor 1 receptor; DNMT, DNA methyltransferase; PSME4, Proteasome activator complex subunit 4; FGFR1, Fibroblast growth factor receptor 1; VEGF, Vascular endothelial growth factor; PSMD10, 26S proteasome non-ATPase regulatory subunit 10; ASF1B, anti-silencing function 1B histone chaperone; Sp1, stimulatory protein 1; CDK6, cyclin dependent kinase 6; MCL-1, myeloid cell leukemia-1; NOTCH1, Notch homolog 1; BCL2, B-cell lymphoma 2; BAFF, B cell activating factor belonging to the TNF family; C-MYC, v-myc avian myelocytomatosis viral oncogene homolog; PIK3α, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; PIK3C2A, phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2α; MDM4, MDM4, p53 regulator; MDM2, MDM2 proto-oncogene; IL, interleukin; PIM-1, pim-1 proto-oncogene, serine/threonine kinase; GR-α, glucocorticoid receptor α; Refs., references.

associated agonist of cell death, and caspase-9 by reducing the interaction of AKT and its substrate glycogen synthase kinase 3β, which led to the limitation of cell proliferation and an increase of cell apoptosis (62). Because of these significant tumor inhibitory effects, miRNA-29b has potential in clinical application as a micromolecular nucleic acid drug. There have been numerous *in vivo* studies that combine clinical routine chemotherapy drugs with miRNAs. The results concluded that miRNA-29b additionally possesses a strong tumor inhibitory effect *in vivo* (78). In addition, this miRNA family is considered to be associated with complications in MM. Rossi *et al* (79)

revealed that miR-29b expression declined alongside osteoclast differentiation, and its negative regulation of osteoclast activity may overcome the strong pro-osteoclastic stimuli provided by MM cells. Another previous study indicated that the expression of miR-29c is negatively correlated with the severity of renal failure and the expression level of β2-microglobulin (β2-M), but the precise mechanism remains yet to be fully understood (80).

miR-181a/b. miR-181a/b, located in chromosome 1q32.1, is reported to be upregulated in the malignant PCs of MGUS and MM. This upregulation suggests that miR-181a/b may be

Table IV. Studies evaluating the diagnostic values of miRNAs using ROC analysis.

Name	Sample	Sensitivity (%)	Specificity (%)	AUC	Cut-off value	Refs.
miR-720	MM/MG vs. N	87.2	92.3	0.9112	5,773.0000	(85)
miR-1308	MM/MG vs. N	82.1	92.3	0.8920	405,400.0000	(85)
miR-720+miR-1308	MM vs. MG	97.4	92.3	0.9862	83.9000	(85)
miR-1246+miR-1308	MM vs. MG	79.2	66.7	0.7250	6.4000	(85)
miR-29a	MM vs. N	88.0	70.0	0.8320	0.0103	(86)
miR-483	MM vs. N	50.0	90.0	0.7450	12.6900	(87)
miR-20a	MM vs. N	63.0	85.0	0.7400	478.9000	(87)
miR-34a+Let-7e	MM vs. N	80.6	86.7	0.8980	ND	(14)
miR-19a+miR-4254	MM vs. N	91.7	90.5	0.9500	ND	(43)
miR-15a	MM vs. N	100.0	73.0	0.8640	2.3500	(88)
miR-16-1	MM vs. N	78.9	56.7	0.6640	3.1300	(88)
miR-214	MM with BD vs. MM without BD	97.0	86.0	0.7670	ND	(35)
miR-135b	MM with BD vs. MM without BD	100.0	73.0	0.9070	ND	(35)

miRNA/miR, microRNA; ROC, receiving operator characteristic; AUC, area under the curve; MM, patients with multiple myeloma; MG, patients with monoclonal gammopathy of undetermined significance; N, normal controls; BD, bone diseases; ND, not determined; Refs., references.

involved in the primary pathological course of MM (34,38). In MM, the P53 protein may inhibit proliferation and promote the apoptosis of tumor cells. The underlying mechanism may be attributed in part to the fact that P53 may arrest the cell cycle at the G1/S point and accelerating the DNA repairing process. Generally, the P53 gene mutation is observed in the progression from MM to plasma cell leukemia. miR-181a/b serves an important function in regulating P53. A number of studies have revealed that miR-181a/b may negatively regulate the expression of P-300-CBP associated factor (PCAF), antagonize the positive effect of PCAF on P53, and eventually result in the decreased expression of P53 (36). Additionally, miR-181a/b may work as a histone acetyltransferase to keep P53 at a low level or partially inactivated by controlling its stability through human double minute 2. Furthermore, miR-181a/b is abnormally expressed in two drug-resistance MM cell lines (U266 Dox resistant and 8226 Dox resistant) (81), suggesting that miR-181a/b may participate in the drug-resistance course of MM, but the underlying mechanisms remain unclear.

miR-21. miR-21, located in chromosome 17q23.2, is one of the most important onco-miRNAs in MM and its expression is significantly elevated in the malignant PCs of MM (82). miR-21 is closely associated with the bone marrow microenvironment. IL6, secreted by bone marrow mesenchymal stem cells (BMSCs) may induce an elevated expression of miR-21 through activating the STAT3 signaling pathway. Zheng *et al* (83) revealed that, in MM cells, miR-21 expression was positively correlated with an abnormally increased expression of proteasome subunit β4 which may promote the growth and proliferation of MM cells by stimulating the NFκB-miR-21 signaling pathway. miR-21 is not only associated with the malignant behavior of MM cells, but is additionally involved in the drug-resistance behavior of MM cells. It is partly due to the fact that miR-21 may target oncogene ras homolog gene family member B and stimulate the

NFκB signaling pathway, and then overcomes BMSC induced drug-resistance of MM. Increasingly, evidence suggests that miR-21 may become a novel therapeutic target for patients with MM with severe drug-resistance (84).

3. miRNAs as potential diagnostic biomarkers of MM

Bone marrow biopsy is the gold standard for the clinical diagnosis of MM. However, this traditional diagnostic method is invasive and is a painful procedure for patients. It is urgent to identify a more sensitive, convenient and noninvasive biomarker to apply in the clinical diagnosis of MM. ROC curve analysis provides a regular way to assess the value of diagnosis. Here, studies evaluating the diagnostic values of miRNAs have been summarized in Table IV (14,35,43,85-88).

miRNAs may distinguish patients with MM from HDs. Extracellular free miRNAs are protected by tiny vesicles, exosomes, particles and apoptosis bodies, or bind to proteins in serum, plasma, saliva, urine and other body fluids to avoid being degraded (89). This feature means that miRNAs possess the potential to be indicators of MM in clinical applications (90). Jones *et al* (85) obtained a series of miRNAs whose expression differed between patients with MM and HDs through gene array analysis of the peripheral serum in patients with MM and conducted a large-scale validation for three miRNAs (miR-720, miR-1308 and miR-1246) with a relatively large difference of expression between them. ROC curve analysis revealed that serum miR-720 yielded an area under the curve (AUC) of 0.9112 (P<0.001) with 87.2% sensitivity and 92.3% specificity for discriminating patients with MGUS and MM from healthy controls. A combination of miR-1308 and miR-720 provided a more powerful diagnostic effect with the AUC rising to 0.9862, with a sensitivity of 97.4% and specificity of 92.3%. Another previous study indicated that miR-142-5p, miR-660 and miR-29a

were upregulated in the serum of patients with MM (86). Further ROC curve analysis demonstrated that serum miR-29a expression possessed a potent ability in discriminating patients with MM from HDs with an AUC of 0.8320, with 88.0% sensitivity and 70.0% specificity. Qu *et al* (87) discovered that serum miR-483-5p and miR-20a possessed a considerable diagnostic efficacy yielding an AUC of 0.7450 (sensitivity 58.0%, specificity 90.0%) and 0.7400 (sensitivity 63.0%, specificity 85.0%), respectively. Furthermore, a previous study concluded that the combined application of the serum expression of miR-19a with miR-4254 had a significant diagnostic value with an AUC of 0.9500, with a sensitivity of 91.7% and specificity of 90.5% (43).

These studies utilizing ROC analysis suggest that miRNAs possess considerable diagnostic efficacy as serological markers for MM, and have advantages over traditional diagnostic methods, including convenience and noninvasiveness. Despite the fact that the preliminary results are positive, larger samples are required for further validation. Additionally, the methods of specimen collection, RNA extraction and data analysis varied between different studies, and it is necessary to set up a unified standard in the process of testing.

Correlation between miRNAs and clinical parameters of MM. miRNAs are closely associated with the occurrence and development of MM and their expression levels are significantly correlated with a number of common laboratory biomarkers of MM (91). Therefore, miRNAs may be used as indicators to reflect the severity of MM. It was identified that serum miR-214 and miR-135b expression levels had the ability to distinguish between patients with MM with or without bone disease and may reflect the severity of bone lesions (35). The AUC of miR-214 was 0.767 with 97% sensitivity and 86% specificity, and the serum level of miR-135b was a powerful diagnostic tool in the identification of MM associated bone diseases with an AUC of 0.907, sensitivity of 100% and specificity of 73%. Additionally, these two miRNAs were positively correlated with the severity of bone disease. Kubiczkova *et al* (14) revealed that serum miR-744, miR-130a, let-7d, and let-7e levels were positively correlated with hemoglobin levels in patients with MM and the expression levels of miR-744, miR-130a, let-7d, and let-7e were positively correlated with the thrombocyte count and significantly negatively correlated with creatinine and β-2 microglobulin levels. Furthermore, the expression levels of miR-744, let-7d and let-7e were positively associated with albumin levels and miR-744, let-7e were negatively associated with C-reactive protein. Only the let-7e expression was negatively correlated with monoclonal immunoglobulin levels.

miRNAs possess advantages in sensitivity and specificity of detection compared with conventional hematological auxiliary diagnostic indicators. Furthermore, one abnormally expressed miRNA may have a correlation with multiple conventional hematological parameters (14). This quality will increase their convenience for clinical application. A number of miRNAs were also significantly associated with imagological examination. A previous study investigated the ability of miR-214 and miR-135b to distinguish between patients with MM with and without bone disease using the ROC analysis and it was revealed that they possess greater potential as an alternative of imageological examination due to the fact that they are more convenient and economical (35).

4. miRNAs as potential prognostic biomarkers of MM

MM is a hematological tumor with obvious heterogeneity. Patients with different stages and classifications vary in therapeutic strategies and clinical outcomes. Clinical research on the prognosis of MM has been continuously progressing. Presently, commonly used indicators for prognosis of MM are usually based on cytogenetic abnormities including Translocation/Cyclin D (TC), International Staging System (ISS) and fluorescence hybridization (FISH) of malignant PCs, and gene expression profiling (GEP) (92). These classification methods have clinical effectiveness to some extent, but cannot accurately reflect all genetic mutations during the process of MM. miRNAs may regulate almost all cellular processes with a more comprehensive reflection of the dysfunctional state of patients with MM. Therefore, miRNAs are more likely to become novel effective biomarkers for predicting the prognosis of MM patients. Table V (14,15,35,43,87,88,93,94) summarizes studies evaluating the prognostic values of miRNAs using survival analysis.

Correlation of miRNAs and conventional prognostic biomarkers of MM. Wu *et al* (95) analyzed miRNA expression profiling in CD138$^+$ cells from the bone marrow tissues of patients with MM and followed them up. A distinct upregulation of the miRNA cluster miR-99b/let-7e/miR-125a on 19q was identified in TC 4p16 cases, and additionally miR-150/miR-155/miR-34a were upregulated in the MAF subgroup. An outcome scale model was established based on the combined application of miR-17 and miR-886-5p, and patients were divided into high-, moderate- and low-risk groups (P=0.001) according to their overall survival (OS). The prediction accuracy of the combined application of these two miRNAs is 98.46%, much greater than that of the outcome scale approach based on ISS/FISH (P=0.0004). This novel outcome scale mode based on miRNAs was also able to identify that patients with MM carrying the t(4;14) mutation and patients carrying the t(4;14) mutation with a lower expression of these two miRNAs had a longer OS (71 months). Additionally, Huang *et al* (93) conducted FISH tests in malignant PCs and then detected miRNA expression levels in plasma of patients with MM. The expression level of miR-99b in the plasma of patients with MM was revealed to be significantly correlated with t(4;14; immunoglobulin heavy locus; fibroblast growth factor receptor 3) translocation and the low expression of miR-221 was significant associated with del(13q14). Qu *et al* (87) observed the significantly association between plasma miR-483-5p expression levels and the ISS stage. Furthermore, Kubiczkova *et al* (14) revealed that serum miR-744, let-7d, and let-7e expression levels were positively correlated with ISS staging in patients with MM and serum let-7e expression level was significantly associated with del (13q14) obtained from the FISH tests of MM PCs.

These results indicated that miRNAs have a huge potential to function as prognostic indicators. Furthermore, as they may be detected more conveniently, circulating miRNAs may offer an advantage over the traditional FISH detection of malignant PCs in bone marrow.

Survival analyses of miRNAs in MM. In addition to being associated with conventional prognostic markers, long-term follow-up studies may reveal the association between miRNA

Table V. Studies evaluating the prognostic values of miRNAs using survival analysis.

Name	P-value	HR (95% CI)	Method	Refs.
RFS				
miR-20a	0.0100	ND	K-M	(93)
miR-148a	0.0200	ND	K-M	(93)
PFS				
miR-25	0.0340	0.920 (0.840, 0.990)	Univariate Cox regression	(94)
miR-483	0.0250	ND	K-M	(87)
miR-33b	0.0160	ND	Univariate Cox regression	(15)
miR-19	0.0030	2.787 (1.421, 5.468)	Multivariable Cox regression	(43)
miR-15a	0.0080	0.260 (0.090, 0.710)	Multivariable Cox regression	(88)
miR-214	0.0150	ND	K-M	(35)
OS				
miR-25	0.0005	0.810 (0.720, 0.910)	Univariate Cox regression	(94)
miR-25	0.0130	0.760 (0.620, 0.940)	Multivariable Cox regression	(94)
miR-744	0.0001	0.670 (0.548, 0.819)	Univariate Cox regression	(14)
Let-7e	0.0020	0.611 (0.450, 0.829)	Univariate Cox regression	(14)
miR-33b	0.0330	ND	Univariate Cox regression	(15)
miR-19	0.0230	2.995 (1.167, 7.690)	Multivariable Cox regression	(43)
miR-15a	0.0350	0.280 (0.080, 0.930)	Multivariable Cox regression	(88)
miR-214	0.0020	ND	K-M	(35)

miRNA/miR, microRNA; HR, hazard ratio; CI, confidence interval; ND, not determined; RFS, relapse-free survival; PFS, progression-free survival; OS, overall survival; K-M, Kaplan-Meier method; multivariable Cox regression, multivariable Cox proportional hazards regression model, univariate Cox regression, univariate Cox proportional hazards regression model; Refs., references.

expression and the life expectancy of patients with MM directly. Huang *et al* (93) assessed the association between plasma miRNAs and the life expectancy of patients using Kaplan-Meier survival curves. Results demonstrated that high expression levels of plasma miR-20a and miR-148a in patients with MM were significantly correlated with relapse-free survival (P=0.01 and P=0.02, respectively). Rocci *et al* (94) selected ten miRNAs which had stable serum expression for a follow-up study. Results indicated that patients with MM with higher levels of miR-25 [hazard ratio (HR)=0.81; P=0.0005], miR-16 (HR=0.87; P=0.008) and miR-30a (HR=0.86, P=0.016) in their serum had a longer OS than those with a lower expression of these miRNAs. Furthermore, serum miR-25 expression level was significantly correlated with progression-free survival (PFS; P=0.034). Additionally, it was concluded that miR-25 and miR-16 were independent prognostic indicators for the OS of newly diagnosed patients with MM using Cox regression analysis. Hao *et al* (35) reported that the high expression of serum miR-21 may be an effective indicator of the poor outcomes in patients with MM. Patients with high expression level of serum miR-214 had significant shortened PFS (P=0.015) and OS (P=0.002) compared with those with a low expression level.

miRNAs have proved to be effective indicators in survival analysis and risk evaluation. The next step of these studies should focus on validating these biomarkers in larger samples and then combining utilization with conventional prognostic markers including ISS, FISH and GEP to improve the accuracy of risk stratification and outcome prediction.

miRNAs used for predicting of therapeutic response in MM. Patients with MM have varied therapeutic responses and a number of patients are resistant to one or more chemotherapy drugs, which bring a number of difficulties to clinical treatment. It is imperative to discover novel clinical indicators that may effectively predict the therapeutic efficacy. ASCT is a recognized effective therapy for MM, but its therapeutic efficacy remains different for different individuals. Navarro *et al* (96) investigated the difference of serum miRNA expression profiling in patients with MM prior to and following performing ASCT. Results indicated that patients with a high expression of serum miR-19b and miR-331 had significantly prolonged PFS subsequent to receiving ASCT (P<0.001 and P=0.001, respectively) and combined application of these two miRNAs may be a more effective predicting indicator for PFS following ASCT (HR=5.3, P=0.033). Hao *et al* (43) identified that patients with a low expression of serum miR-19a had an improved therapeutic response to bortezomib (BZ) and significantly extended PFS and OS following BZ treatment (P=0.002), whereas patients with a high expression of serum miR-19a had no obvious efficacy and no improvement in survival analysis. Li *et al* (88) investigated whether miR-15a downregulated in bone marrow tissues may influence the response of patients to different therapies. It was revealed that therapy based on thalidomide and BZ may not remarkably improve the PFS and OS of patients with a low-expression of miR-15a. Another previous study on miRNA expression profiling analysis associated with serum exosomes revealed that the expression levels of serum exosome derived miR-16-5p, miR-15a-5p, miR-20a-5p and miR-17-5p

had increased 3.91, 1.83, 2.96 and 1.97 times, respectively, in the BZ-effective group compared with those in the BZ-resistant group (97).

These previous studies suggest that different miRNA expression profiling are significantly associated with the varied therapeutic responses of patients and may be used as predicting indicators to monitor therapeutic responses in patients with MM. In addition, these miRNAs may also provide an important basis for individual treatment.

Dynamics of miRNA levels during MM progression. As deregulated miRNA expression in patients with MGUS and MM was observed at the time of diagnosis, the further aim for researchers was to check if this profiling changed during disease progression. Kubiczkova *et al* (14) collected serum samples at the time of diagnosis and relapse (following 2 lines of treatment), and revealed that almost all miRNAs in MM samples were significantly different from HDs (miR-744: FC=0.270, miR-130a: FC=0.487, miR-34a: FC=10.083, let-7d: FC=0.243, let-7e: FC=0.300). Furthermore, a significant increase of miR-34a (P<0.0001, FC=3.560) and decrease of let-7d (P=0.0182, FC=0.460) were revealed in relapsed samples compared with samples at the time of first diagnosis. Yyusnita *et al* (40) claimed that four miRNAs (miR-494, 130a, let-7i, let-7c) in peripheral blood samples were exclusively expressed in novel MM cases whereas nine (miR-148a, 1225, 423, 484, 99a, 106a, 224, 638, let-7b) were exclusively expressed in follow-up MM cases. Hao *et al* (43) indicated that miR-19a and miR-4254 expression levels were closer to the levels in HDs when in a remission phase. However, downregulated miR-19a and upregulated miR-4254 levels returned to diagnostic levels during relapse. These results demonstrated that the expression of miRNAs varied in patients with different stages of MM and had utility in monitoring MM progression.

5. miRNA-based therapeutic strategies in MM

With the exception of ASCT, traditional therapies of MM are usually based on the combined treatment of multiple chemotherapy drugs, including immunomodulatory drugs (lenalidomide and thalidomide), proteasome inhibitors (BZ), alkylating agents (melphalan and cyclophosphamide), and steroid hormones (dexamethasone). In spite of advances in present therapies, a low remission rate and drug-resistance towards the traditional chemotherapy regimen in patients with MM often result in difficulties in the clinical cure of this disease. Multiple signaling pathways may enhance the growth, proliferation, survival and migration of MM cells, and additionally induce the drug-resistance of MM cells in the pathological process of MM (98). miRNA-based therapy may selectively downregulate genes involved in the pathological processes of MM. In addition to targeting genes effectively, this therapy has the advantage of being safer. Gallo Cantafio *et al* (99) studied the pharmacokinetics and pharmacodynamics of the 13-merLNA-inhibitor-miR-221. The results of this previous study indicated that LNA-i-miR-221 harbored a short half-life, optimal tissue bioavailability and minimal urine excretion in mice and monkeys and revealed no toxicity in the pilot monkey study. Therefore, miRNA-based therapy is a promising novel therapeutic method for MM (100,101).

miRNAs as novel drugs used in MM. miRNAs may regulate the growth of tumor cells through suppressing target gene expression. This therapeutic strategy has proved effective *in vivo* by an increasing number of studies. Di Martino *et al* (65) confirmed that miR-34a had a significant tumor inhibitory effect on severe combined immunodeficient (SCID) mice. First, miR-34a was proved to downregulate oncogenic expression, including BCL2, apoptosis regulator, cyclin dependent kinase 6 and Notch 1, at mRNA and protein levels *in vitro*. MM cells overexpressed miR-34a demonstrated growth inhibition, low colony formation activity and increased apoptosis. Next, in *in vivo* studies, researchers conducted a xenograft tumor experiment through transfecting MM cells with lentiviral miR-34a over-expression vector then injecting these cells in SCID mice. Lentiviral vector-transduced MM xenografts with constitutive miR-34a expression demonstrated high growth inhibition in SCID mice with a significant inhibition of tumor formation (P<0.05) and the decrease of the tumor average size (P=0.008). Subsequently, in order to investigate the anti-tumor effect of lipid-formulated miR-34a, miR-34a or miR-NC were administered into neutral lipid emulsion (NLE) particles and make a systemic delivery of oligonucleotides in mice. Results indicated that, after 21 days, tumors were inhibited in 50% of mice treated with formulated miR-34a mimics. In addition, a prolongation of survival time (P=0.0009) was observed in mice treated with miR-34a mimics compared with control groups. Additionally, a biopolymeric 3D scaffold constructed by MM cells and BMSCs was implanted into SCID mice to simulate a bone marrow microenvironment-dependent effect on MM cells. The significant inhibition of tumor growth (P<0.01) and prolonged survival (P=0.041) were observed in mice with miR-34a overexpression, which indicated that miR-34a may overcome the protective function of BMSCs for MM cells and suppress tumors.

Therapeutic effects of miRNAs were dependent on different vectors, including lentivirus, liposome and NLE. Furthermore, compared with traditional chemotherapeutic drugs, miRNAs have the obvious therapeutic efficacy *in vivo* without toxic reaction, release of inflammatory factors or other drug side effects.

Advantages of combined application of miRNAs and chemotherapy drugs. Previous studies indicated that the combined use of chemotherapy drugs and miRNAs may improve the therapeutic efficacy compared with a single application of one miRNA or chemotherapy drug and reduced drug-resistance of traditional chemotherapy drugs.

Glucocorticoid (GC) is frequently included in the chemotherapeutic regimen for lymphoid malignant tumors because of its capability for killing lymphoid cells. In the long-term, high-dose GC will result in the reduction of glucocorticoid receptors (GR), and then induce resistance to GC. However, low-dose GC does not have enough therapeutic efficacy. Palagani *et al* (102) investigated the possibility of improving this situation using a miRNA combined application with GC. The results of this previous study confirmed that the miR-150 synthetic vector combined with low-dose GC had a synergistic therapeutic effect on MM cells by markedly raising the cell sensitivity for GC-induced death. Furthermore, miR-150 may induce the specific response of GR via indirectly regulating the mRNAs of the proteins interacting with GR, including hormone receptors, molecular chaperones, unfolded protein stress and transcriptional

factors, so that resistance to GC is unlikely to occur. In addition, miR-150 in tiny vesicles may also be considered to be a monitoring biomarker of therapeutic response to GC (103). Zhao *et al* (50) reported that mir-221/222 family expression was elevated in GC-resistance cell lines MM1R and further study verified that this miRNA family reduced the drug-resistance of MM cells to dexamethasone (Dex) and promoted the survival of MM cells by BCL2 binding component 3/BCL2 antagonist/killer 1/BCL2 associated X, apoptosis regulator signaling pathway. Therefore, miR-221/222 antagonists may be promising therapeutic targets for reversing the drug-resistance of MM cells to Dex. Subsequently to the construction of a xenograft tumor model in SCID mice, mice treated with miR-221/222 antagonist and Dex had significantly longer survival than the mice treated only with Dex (P<0.05). In addition, Gulla *et al* (48) reported that the inhibition of miR-221/222 may restore melphalan sensitivity in MM and induced apoptosis of MM cells *in vitro*. It was also revealed LNA-i-miR-221 may perform anti-MM activity by systemic delivery *in vivo*. They demonstrated the rationale of the combined use of LNA-i-miR-221 and melphalan in drug-refractory stage of patients with MM.

BZ may inhibit the formation of proteasome, so that misfolded and short-lived proteins may not be eliminated, leading to the death of tumor cells eventually. At present, BZ has been widely used in the standard treatment regimen of MM, but BZ has a number of side effects. For example, the enhanced accumulation of polyubiquitin in cells results in an increase of protein aggregation and autophagosome to eliminate excessive polyubiquitin. This autophagy behavior eventually contributes to the occurrence of drug-resistance in tumor cells. Therefore, it is warranted to seek a type of chemotherapy drug that may eliminate proteasomes in cells without increased protective autophagy behavior. Jagannathan *et al* (59) identified that the increased expression of miR-29b reinforced the BZ-induced aggregation of polyubiquitin without inducing the formation of a protein autophagosome. miR-29b may result in proteasome degradation and cell death by targeting proteasome activator subunit 4, and this pattern does not affect the accumulation of ubiquitinated proteins and is different from the mechanism of BZ-induced proteasome degradation. Additionally, the combined application of miRNA with BZ may decrease drug-resistance to BZ. A previous study concerning miR-29b and BZ disclosed that miR-29b with transcription factor Sp1 transcription factor may increase the sensitivity of MM cells to BZ and led to the increased apoptosis of MM cells through the PI3K-AKT signaling pathway (62). The group treated with BZ and miR-29b had a significantly enhanced effect on cell apoptosis, compared with the control group (P<0.01). Furthermore, Wang *et al* (84) reported that miR-21 combined with BZ, Dex, and doxorubicin (Dox) had a synergistic effect in killing MM cells and were demonstrated to be more effective than the application of any drug alone.

PRIMA-1^Met is a novel micromolecular chemotherapy drug (104). The therapeutic efficacy of the combination of PRIMA-1^Met with miR-29a for MM treatment was previously studied (105). miR-29a was considered to be a TS-miRNA and served an important function in the PRIMA-1^Met induced cell apoptosis by targeting the C-MYC gene. Further xenograft tumor experiments on SCID mice verified that miR-29a combined with PRIMA-1^Met may significantly inhibit the growth of tumors and the extended survival time of SCID mice, which provided a novel therapeutic strategy for the treatment of MM.

Preliminary basic studies of miRNAs in the treatment of MM have made progress, but its clinical application remains in its infancy and faces several challenges. Tumor formation and treatment duration in animal models are markedly different from those in human beings. It remains unclear if miRNAs exert a similar effect and long-term function in human beings. Furthermore, vectors that deliver miRNAs *in vivo* remain to be improved. It should be ensured that during the process of delivering, carriers are safe and produce no toxic or other side effects, and transported nucleic acid molecules are stable without degradation by endogenic nuclease, which requires more effective chemical modification technology to improve current vectors for clinical application.

6. Conclusion

Basic studies of tumors has always been an area of concentrated research, but the transformation from preliminary basic studies to clinical application is a problem at present. A number of researchers put forward the concept of 'Theragnostics', representing cutting-edge, multi-disciplinary strategies that combine diagnostics with therapeutics in order to generate personalized therapies and improve the outcomes of tumor patients (13). Application of theragnostics in patients with clinical cancer may raise their survival rate, with a more accurate diagnosis of cancer and optimized choice of treatment regimen.

Circulating miRNAs possess potential to become novel biomarkers obtained in a non-invasive manner (106), but the origin they derive from is still unclear. Furthermore, which is the best detection source out of whole blood, plasma, serum and exosomes remains controversial (89). Kubiczkova *et al* (14) discussed the derivation of several miRNAs in the exosomal and exosome-depleted supernatant of six newly diagnosed patients with MM. Concentration of miR-744, miR-130a, let-7d and let-7e (all P<0.05) were revealed to be significantly higher in the exosome pellet compared with the exosome-depleted supernatant. Previous studies considered that exosomal miRNA profiling was superior for detecting pathology in secretory cell types. In addition, there remains a lack of standardized protocols for sample collection, small RNA extraction and data-analytical methods when quantifying miRNAs.

miRNAs and their target genes represent basic networks, regulating a variety of cellular functions and that are also the rationale of miRNA-based therapeutic strategies. However, there are multiple miRNAs targeting the same gene, thus interfering with a single miRNA may not produce enough effects; correspondingly, one miRNA may work on multiple targets, which will result in unknown side effects in the long term. Furthermore, in the delivery system, it is necessary to ascertain the right way to inject these vectors to achieve the highest efficacy in the safest manner.

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Authors' contributions

BZ wrote the initial draft and designed the outline of the manuscript. HCo, SJ and XS designed the outline and revised the manuscript. HCh revised and expanded the manuscript. YZ and XL contributed to the acquisition and analysis of data for the work. All authors have seen and approved the final manuscript.

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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