Identification and integrative analysis of microRNAs in myelodysplastic syndromes based on microRNAs expression profile

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Abstract
Myelodysplastic syndromes (MDS) are a group of malignant hematological disorders characterized by the abnormal development of hematopoietic stem cells and increased risk of acute myelogenous leukemia. Although the pathogenesis of MDS has not been fully understood, various alterations of microRNAs (miRNAs) have been reported in MDS. This study aimed to explore the molecular mechanisms of MDS by integrative bioinformatics analysis of miRNAs expression profile. The GSE81372 expression profile dataset was downloaded from Gene Expression Omnibus database. The differentially expressed miRNAs (DEMs) between MDS and normal controls were identified and targets of miRNAs were predicted. Subsequently, gene ontology (GO) functional and pathway enrichment analyses of target genes were performed. Finally, pathway relation network and miRNA–GO regulatory network were constructed and analyzed. A total of six upregulated and 35 downregulated DEMs were identified. The results showed that target genes of DEMs mainly participated in the process of signal transduction, blood coagulation, apoptotic process, cell proliferation, transmembrane transport, and angiogenesis. The significantly enriched pathways included MAPK signaling pathway, PI3K-Akt signaling pathway, TGF-beta signaling pathway, Hippo signaling pathway, and P53 signaling pathway. Moreover, miR-195-5p, miR-4505, miR-22-3p, and miR-148a-3p were selected as hub miRNAs in miRNA–GO regulatory network and their aberrant expression might be closely associated with MDS pathogenesis. Our discovery provides a registry of miRNAs and pathways that are disrupted in MDS, which has the potential to be used in clinic for diagnosis and target therapy of MDS in future.

KEYWORDS
bioinformatics, expression profile, miRNAs, myelodysplastic syndromes, signaling pathway

1 | INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of malignant clonal hematological disorders characterized by inefficient hematopoiesis, unilineage or multi-lineage dysplasia, and increased risk to progression to acute myelogenous leukemia (AML).1 Current known risk factors of MDS include aging, chemotherapy or radiation treatment, occupational exposure and some genetic syndromes such as Fanconi’s anemia.2,3 The somatic gene mutations, epigenetic deregulation, microenvironmental and immune changes have been proven to be critical...
MicroRNAs (miRNAs) are short noncoding RNA molecules that repress expression of genes by inhibiting translation or inducing degradation of target mRNA at the posttranscriptional level. miRNAs regulate numerous biological processes such as proliferation, apoptosis, and differentiation. In addition, miRNAs can be either oncogenes or tumor suppressors in the pathogenesis of different cancers, which may be due to the fact that over half of miRNA genes are located in cancer-related genomic regions.

In recent years, increasing studies have shown that miRNAs are implicated in normal hematopoiesis, and dysregulation of miRNA has been found in hematological malignancies including MDS. It is relatively little known about miRNAs in pathogenesis, prognosis, and therapy of MDS. In the present study, we applied an integrative bioinformatics approach to analyze the miRNAs expression profiles of MDS. We aimed to provide a systematic perspective toward understanding molecular mechanisms and exploring new therapeutic targets for MDS.

2 | MATERIALS AND METHODS

2.1 | Microarray data

The microarray expression profile GSE81372 was downloaded from Gene Expression Omnibus database, which was based on the GPL16384 Affymetrix Multispecies miRNA-3 Array platform. The dataset contained the miRNAs expression profiles of bone marrow CD34+ cells from 12 MDS patients and six normal controls, which was deposited by Xu et al.11

2.2 | Differential expression analysis

The raw data were firstly preprocessed using the Affy package, then the probe-level data in CEL files were converted into expression value matrix. Data preprocessing was performed using robust multiarray average algorithm, including background correction, quartile data normalization, and probe summarization. The significance analysis of microarray method was used to identify the differentially expressed miRNAs (DEMs) between MDS patients and normal controls. Only miRNAs with \( p < .05 \) and \( \text{fold-change} > 2 \) were considered as DEMs. Hierarchical cluster analysis was performed and cluster dendrogram was constructed to assess the characterizations of screened DEMs.

2.3 | Target genes prediction of miRNAs

Interactions between miRNA and mRNA were predicted based on the TargetScan and miRanda databases. The intersections recognized by two main algorithms were considered as candidate target genes of DEMs.

2.4 | Functional enrichment analysis

Gene ontology (GO) analysis was applied to explore the main functions of target genes of DEMs identified in this study. Specifically, two-side Fisher's exact test was used to classify GO category and the false discovery rate (FDR) was calculated using Benjamini–Hochberg method to correct the \( p \) value. FDR < 0.05 was set as the threshold value to select significant GO categories. Besides, the enrichment score was calculated to access the enrichment level for each GO category.

2.5 | Pathway enrichment analysis

Kyoto Encyclopedia of Genes and Genomes (KEGG) knowledge database was used for the classification of correlative gene sets into their respective pathways. The Fisher's exact test was used to calculate the significance \( p \) value and Benjamini–Hochberg procedure was used to calculate FDR. FDR < 0.05 was used as the cutoff criteria to identify the significant pathways. The enrichment score was also calculated to access the enrichment level for each pathway.

2.6 | Pathway network analysis

The network of the significantly enriched pathways was built according to the interaction between pathways among the KEGG database. Each pathway in the network was measured by counting the number of upstream and downstream pathways, which were shown as in-degree or out-degree, respectively.

2.7 | miRNA–GO network analysis

The relation between significant GO items and target genes can be got via GO enrichment analysis, then we can get the relevance between miRNAs and significant GO items based on the fact that miRNA can combine with 3’-UTR of target mRNA. The adjacent relation matrix of GO items and miRNAs was built, and we evaluated the degrees of miRNAs and GO items in the network using the methods of graph theory. Those who had the highest degree were the core miRNAs or GO items.

3 | RESULTS

3.1 | DEMs identification

After data processing, a total of 41 miRNAs, six upregulated and 35 downregulated, were identified to be differentially expressed in MDS patients compared with normal controls (Table 1). The
hierarchical cluster analysis showed that the 12 MDS samples distributed in MDS cluster and six normal samples in control cluster, and no overlap was found between them (Figure 1). This observation showed that separation of the miRNAs expression profiles between MDS and normal controls.

### 3.2 Targets prediction of miRNAs

In present study, targets of these DEMs were identified based on sequence complementarities and free energy of the predicted RNA duplex using TargetScan and miRanda. In total, 71,767 target mRNAs

| Accession    | Transcript ID | Fold change | p value | miRNA feature |
|--------------|---------------|-------------|---------|---------------|
| MIMAT0015055 | hsa-miR-3178  | −8.28       | .003    | Down          |
| MIMAT0000074 | hsa-miR-19b-3p| 2.96        | .004    | Up            |
| MIMAT0000243 | hsa-miR-148a-3p| −3.11      | .004    | Down          |
| MIMAT000437  | hsa-miR-145-5p| −3.28       | .005    | Down          |
| MIMAT0004614 | hsa-miR-193a-5p| −2.39      | .008    | Down          |
| MIMAT0019044 | hsa-miR-4507  | −2.33       | .008    | Down          |
| MIMAT015086  | hsa-miR-3201  | −4.41       | .009    | Down          |
| MIMAT0019739 | hsa-miR-4665-5p| −2.93      | .011    | Down          |
| MIMAT0019069 | hsa-miR-4530  | −2.59       | .011    | Down          |
| MIMAT0019045 | hsa-miR-4508  | −2.47       | .012    | Down          |
| MIMAT0000077 | hsa-miR-22-3p | −2.49       | .013    | Down          |
| MIMAT0000073 | hsa-miR-19a-3p| 4.38        | .013    | Up            |
| MIMAT0004611 | hsa-miR-195-5p| 3.44        | .016    | Up            |
| MIMAT0003326 | hsa-miR-663a  | −3.18       | .016    | Down          |
| MIMAT0017994 | hsa-miR-3615  | −2.30       | .016    | Down          |
| MIMAT0019077 | hsa-miR-1587  | −2.31       | .017    | Down          |
| MIMAT0019032 | hsa-miR-4497  | −2.12       | .018    | Down          |
| MIMAT0004774 | hsa-miR-501-3p| −2.65       | .019    | Down          |
| MIMAT0002888 | hsa-miR-532-5p| −2.58       | .019    | Down          |
| MIMAT0015079 | hsa-miR-3195  | −2.38       | .020    | Down          |
| MIMAT0019041 | hsa-miR-4505  | −3.85       | .021    | Down          |
| MIMAT0018961 | hsa-miR-4443  | −3.37       | .021    | Down          |
| MIMAT0000617 | hsa-miR-200c-3p| −2.89      | .025    | Down          |
| MIMAT0019878 | hsa-miR-4745-5p| −2.27      | .025    | Down          |
| MIMAT0004792 | hsa-miR-92b-5p| −2.71       | .026    | Down          |
| MIMAT0018985 | hsa-miR-3135b | −3.41       | .026    | Down          |
| MIMAT0019019 | hsa-miR-4485  | −8.07       | .026    | Down          |
| MIMAT0000071 | hsa-miR-17-3p | 2.51        | .028    | Up            |
| MIMAT0003339 | hsa-miR-421   | −2.81       | .029    | Down          |
| MIMAT0004559 | hsa-miR-181c-3p| 2.48        | .031    | Up            |
| MIMAT0004775 | hsa-miR-502-3p| −2.18       | .031    | Down          |
| MIMAT0002871 | hsa-miR-500a-3p| −2.03      | .037    | Down          |
| MIMAT0000424 | hsa-miR-128-3p| −2.86       | .037    | Down          |
| MIMAT0004568 | hsa-miR-221-5p| 2.20        | .038    | Up            |
| MIMAT0019745 | hsa-miR-4668-5p| −2.44      | .040    | Down          |
| MIMAT0016915 | hsa-miR-4284  | −2.52       | .041    | Down          |
| MIMAT0000705 | hsa-miR-362-5p| −2.49       | .041    | Down          |
| MIMAT0005951 | hsa-miR-1307-3p| −2.95      | .045    | Down          |
| MIMAT0001339 | hsa-miR-422a  | −3.19       | .046    | Down          |
| MIMAT0002872 | hsa-miR-501-5p| −2.12       | .048    | Down          |
| MIMAT0000762 | hsa-miR-324-3p| −2.65       | .048    | Down          |

Abbreviations: MDS, myelodysplastic syndromes; miRNAs, microRNAs.
were obtained by miRanda, and 26,301 target mRNAs were obtained by TargetScan; a total of 56,411 target mRNAs overlapped between two datasets (Table S1).

### 3.3 Functional enrichment analysis

In order to functionally annotate the target genes, we performed GO enrichment analysis. The result revealed that a total of 754 GO terms for biological processes were significantly impacted by target genes under the threshold of FDR < 0.05. The top 20 significant GO categories were shown in Figure 2. We identified GO terms significantly enriched in regulation of transcription, signal transduction, protein phosphorylation, axon guidance, blood coagulation, apoptotic process, cell proliferation, transmembrane transport, transforming growth factor (TGF) beta receptor pathway, and angiogenesis. For molecular functions, the enriched GO terms were protein binding, DNA binding, transcription factor activity, protein kinase activity, protein dimerization activity, signal transducer activity, and ubiquitin ligase activity (Table S2).

### 3.4 Pathway enrichment analysis

As shown in the results, the target genes were enriched in a total of 126 significant pathways under the threshold of FDR < 0.05. The top 20 significant pathways were shown in Figure 3. The significantly enriched pathways included pathways in cancer, MAPK signaling pathway, PI3K-Akt signaling pathway, TGF-beta signaling pathway, Hippo signaling pathway, Insulin signaling pathway, focal adhesion, and P53 signaling pathway (Table S3).

### 3.5 Pathway network analysis

To systematically understand the central pathways involved in MDS pathogenesis, we constructed the network of significant pathways according to the relationship provided by KEGG pathway database. As shown in Figure 4, the main pathways implicated in MDS were MAPK signaling pathway, cell cycle, P53 signaling pathway, and Wnt signaling pathway. Degree number of pathways in the network represented their interconnection complexity with other pathways. The degree numbers of top 10 significant pathways were shown in Table 2.
3.6 | miRNA–GO network analysis

In order to clarify the regulatory status of miRNAs and GO items, a miRNA–GO network was built according to interactions between miRNAs and GO items (Figure 5). The network provided us with the key drivers of MDS, including miR-195-5p, miR-4505, miR-22-3p, and miR-148a-3p. It was also noticed that blood coagulation was the core GO items with the highest degree in the network. The top 10 significant DEMs identified by miRNA–GO network were shown in Table 3.

4 | DISCUSSION

miRNAs are essential regulators of the development of hematopoietic stem cells (HSCs). Therefore, alterations of these miRNAs may affect proliferation and differentiation of HSCs, contributing to the pathogenesis of hematological malignancies, including MDS.19,20

Accumulating evidences have strongly suggested that miRNAs are critical in the pathogenesis of MDS, and that dysregulation of miRNAs and other molecular defects cooperate to cause MDS, providing a promising method for the treatment of MDS.21,22
In this study, we focused on investigating the potential miRNAs of MDS by analyzing the miRNAs expression profile between MDS and normal controls. A total of six upregulated and 35 downregulated DEMs were identified and the targets of these DEMs were identified. The GO enrichment analysis showed that target genes of DEMs mainly participated in the process of signal transduction, blood coagulation, apoptotic process, cell proliferation, TGF-beta receptor signaling pathway and angiogenesis. The significantly enriched pathways that target genes participated in included MAPK signaling pathway, PI3K-Akt signaling pathway, TGF-beta signaling pathway, Hippo signaling pathway, and P53 signaling pathway. These results suggested that MDS progression was strongly associated with (1) cell proliferation, apoptosis and angiogenesis, (2) cell adhesion, (3) the imbalance of oncogenes and cancer suppressors as well as (4) the immune dysfunction.

Our results of pathway analysis and pathway network indicated that MAPK signaling pathway was the key pathway involved in MDS carcinogenesis. MAPK is responsible for the control of gene expression programs activated by HSPC-produced cytokines, therefore, its deregulation in MDS exerts a direct effect on hematopoiesis. The use of a P38 MAPK inhibitor in low-risk MDS is strongly supported by the finding that these patients have increased p38 MAPK phosphorylation in hematopoietic progenitor cells of all myeloid lineages and

**TABLE 2** The top 10 significant pathways identified by pathway network according to degree number

| Pathway ID | Pathway name                  | Outdegree | Indegree | Degree |
|------------|-------------------------------|-----------|----------|--------|
| 04010      | MAPK signaling pathway        | 4         | 35       | 39     |
| 05200      | Pathways in cancer            | 27        | 0        | 27     |
| 04110      | Cell cycle                    | 2         | 20       | 22     |
| 04310      | Wnt signaling pathway         | 7         | 10       | 17     |
| 04520      | Adherens junction             | 6         | 11       | 17     |
| 04115      | P53 signaling pathway         | 1         | 15       | 16     |
| 04012      | ErbB signaling pathway        | 8         | 6        | 14     |
| 04020      | Calcium signaling pathway     | 4         | 10       | 14     |
| 04510      | Focal adhesion                | 7         | 7        | 14     |
| 04350      | TGF-beta signaling pathway    | 3         | 9        | 12     |

**FIGURE 4** Pathway network analysis of the significant pathways. The circle represents the pathway, and the lines show the interaction between pathways.
that these phosphorylation levels are positively correlated with the rate of intramedullary apoptosis.\textsuperscript{24,25}

In accord with previous studies, Wnt activation may also contribute to the pathogenesis of MDS. Gene expression profiling of hematopoietic cells supports a role for Wnt pathway activation in MDS, AML, and therapy-related myeloid neoplasms.\textsuperscript{26} Moreover, Wnt activation in HSCs has been directly implicated in self-renewal of leukemia stem cells, and is associated with a poorer outcome in AML patients.\textsuperscript{27} In addition, we also found VEGF signaling pathway was significantly enriched in MDS, suggesting that angiogenesis was extensively implicated in carcinogenesis. The imbalance of oncogene and cancer suppressor was a crucial mechanism of MDS progression, such as the mutations of TP53 gene have an unfavorable prognosis in MDS.\textsuperscript{28} Taken together, these pathways and genes involved in tumor cell proliferation, apoptosis, self-renewal and angiogenesis might be taken as diagnostic biomarkers and potential therapeutic targets for MDS.

Pathway analysis identified that focal adhesion, adhesion junction and calcium signaling pathway were enriched. Emerging evidence point to bone marrow microenvironment (BMME) abnormalities as central participants in the progression of MDS pathogenesis whereby, (1) BMME abnormalities contribute to the development and expansion of MDS clones, (2) MDS cells further modify the BMME via aberrant production of cytokines, and (3) a dysfunctional BMME further promotes clonal expansion and disease progression.\textsuperscript{29,30} The presence of aberrant inflammatory signaling in MDS is supported by numerous studies describing altered levels of inflammatory cytokines in MDS bone

**TABLE 3** The top 10 significant miRNAs identified by miRNA-GO network according to degree number

| Transcript ID | miRNA feature | Degree |
|---------------|---------------|--------|
| hsa-miR-195-5p | Up            | 433    |
| hsa-miR-4505  | Down          | 379    |
| hsa-miR-22-3p | Down          | 373    |
| hsa-miR-148a-3p | Down   | 360    |
| hsa-miR-145-5p | Down         | 348    |
| hsa-miR-200c-3p | Down   | 342    |
| hsa-miR-3135b | Down          | 324    |
| hsa-miR-128-3p | Down          | 316    |
| hsa-miR-4530  | Down          | 305    |
| hsa-miR-19a-3p | Up            | 295    |

Abbreviations: miRNAs, microRNAs; miRNA-GO, microRNA–gene ontology.
Further understanding of the multidirectional relationships between MDS and the diverse cells within the hematopoietic niche is needed to delineate the mechanisms underlying hematopoietic failure.

miR-195-5p, miR-4505, miR-22-3p, and miR-148a-3p were selected as hub miRNAs in miRNA-GO regulatory network and their aberrant expression might be closely associated with MDS pathogenesis. miR-195-5p was upregulated while DLL1 was downregulated in patients with low-grade MDS compared with normal controls. Luciferase assay showed that DLL1 was a direct target of miR-195-5p, and inhibition of Notch signaling pathway by miR-195-5p-DLL1 axis contributes to the excess apoptosis in low-grade MDS.11 Macrophages overexpressing miR-148a-3p increased their ROS production through the PTEN/AKT pathway, likely to defend against bacterial invasion. Moreover, miR-148a-3p also enhanced M1 macrophage polarization and pro-inflammatory responses through PTEN/AKT-mediated upregulation of NF-κB signaling.12

However, there were several limitations of the present study. First, our study was limited to the small amount of data. Therefore, a meta-analysis including larger sample sizes may be performed in future. Second, the results were not verified by biological experiments. Thus, further experimental studies are still needed to confirm the findings of this study.

5 | CONCLUSIONS

In summary, our results provide a comprehensive bioinformatics analysis of miRNAs and pathways which may be involved in the carcinogenesis of MDS. Our findings may be helpful for understanding the complex mechanisms underlying MDS and guiding the development of targeted therapies for patients with MDS.

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CONFLICT OF INTEREST

The authors have no competing interest to disclose.

AUTHOR CONTRIBUTION

Haiping Yang contributed to the conception of the study and helped perform the analysis with constructive discussions. Limin Ma performed the experiment and performed the data analyses and wrote the manuscript. Xuewen Yang contributed significantly to analysis and manuscript preparation.

ETHICS STATEMENT

This study does not involve medical ethics.

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SUPPORTING INFORMATION
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