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Original Article

MicroRNAs and regulated interaction networks reveal differences between adult and pediatric acute myeloid leukemia

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Abstract: Objectives: The purpose of this study was to identify featured microRNAs and their regulated network between adult and pediatric acute myeloid leukemia (AML) and find potential utility as biomarkers for diagnosis and treatment of pediatric AML. Methods: We downloaded the microRNA expression dataset GSE35320 from Gene Expression Omnibus database and selected expression chips from bone marrow of 71 pediatric AML samples and 6 adulthood AML samples. Differentially expressed microRNAs were identified by Wilcox test. The target genes of these microRNAs were predicted using an integrative method and their functional enrichment analysis was performed using DAVID. Finally, STRING database and Cytoscape software was used to construct and analyze the interaction network. Results: A total of 7 differentially expressed microRNAs were identified and the remarkably up-regulated and down-regulated microRNAs were miR-16 and miR-142-5p which included 323 and 22 predicted target genes, respectively. The target genes of 7 microRNAs were most associated with regulation of cell cycle, p53 signaling pathway, Wnt signaling pathway and neurotrophin signaling pathway. The interaction network of miR-16 target genes was constructed among 354 high confidence interaction pairs. The core genes of the network, such as TP53, BCL2, VEGFA, had a role in prognosis of children with AML. Conclusions: The featured microRNAs and their target genes are significant in the occurrence and development of pediatric AML, which is likely to be important for the identification of therapeutic targets and biomarkers for these patients.

Keywords: Pediatric acute myeloid leukemia, microRNA, differential expression, interaction network, miRNA-targeted therapy

Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy that is the second most common type of leukemia in children and accounts for 15-20% of leukemia in children [1]. With advances in chemotherapy and hematopoietic stem cell transplantation, treatment outcome and prognosis of pediatric AML have been greatly improved and the overall survival (OS) rates are now approaching approximately 70% [2, 3]. However, the prognosis for certain high-risk groups of AML and relapsed disease remains poor. There is still considerable need for novel, targeted therapies to further improve the treatment outcome of this disease.

MicroRNAs (miRNAs), a class of about 22 nucleotide-long noncoding RNAs, regulate gene expression at post-transcriptional level and have been predicted to silence over 60% of mammalian genes [4]. They are involved in a variety of critical biological processes and show aberrant expression patterns and functional abnormalities in cancers. Their expression pattern could be used as diagnostic and prognostic biomarkers, as well as oncogenic (or tumor-suppressive) molecules [5]. In adult AML, the roles of microRNAs have been frequently reported. For instance, the miR-29 family that were down-regulated in adult AML samples could function as tumor suppressors, thus their target genes Akt2 and CCND2 that are involved

Table 1. Reported microRNAs in pediatric AML

microRNA	Expression pattern	Function	Reference
miR-100	Up	Prognostic biomarker	Bai et al. [25]
miR-125b	Up	Contribute to leukemogenesis and increases drug resistance in pediatric acute promyelocytic leukemia.	Zhang et al. [34]
miR-155, miR-196b	Up	Diagnostic biomarker	Yan et al. [24]
miR-155	Up	Diagnostic and prognostic biomarker	Xu et al. [35]
miR-181a	Up	Regulate G1/S transition and cell proliferation by regulating ATM,	Liu et al. [36]
miR-335	Up	Biomarker for monitoring progression and predicting the clinical outcome	Lin et al. [37]
miR-375	Up	Prognostic biomarker	Wang et al. [38]
miR-99a	Up	Oncogenic microRNA via regulating tumor suppressors CTDSPL and TRIB2	Zhang et al. [39]
miR-9	Down	Tumor suppressor	Emmrich et al. [40]
miR-139-5p	Down	Tumor suppressor in AML by controlling protein translation	Emmrich et al. [41]
miR-370	Down	Diagnostic and prognostic biomarker	Lin et al. [42]
miR-663	Down	Hyper-methylation of the miR-663 promoter may be an early event in the development of pediatric AML	Yan et al. [43]
miR-126, -146a, -181a/b, -100, and miR-125b	-	Distinguish cytogenetic subgroups in pediatric AML	Daschkey et al. [44]
miR-128a, -128b, -223, and let-7b	-	Discriminate ALL from AML cases	Mi et al. [45]
miR-100, miR-125b, miR-335, miR-146a, and miR-99a	-	Highly expressed in pediatric AML when compared with ALL	Zhang et al. [46]

ALL: Acute lymphoblastic leukemia.

Table 2. Differentially expressed microRNAs (P<0.05 and |FC|>1.5)

microRNA	log (Fold change)	*p*-value	Targets
miR-16	3.50	0.0450	323
miR-221	2.04	0.0112	162
miR-10a	1.10	0.0002	191
let-7b	1.03	0.0026	137
miR-92a	0.93	0.0080	169
miR-26b	-0.86	0.0020	525
miR-142-5p	-4.40	0.0005	22

in the regulation of cell proliferation and cell apoptosis were up-regulated [6]. Low expression level of miR-193b represses AML cell proliferation [7]. Garzon et al. demonstrated that several microRNA signatures were associated with cytogenetic and molecular abnormalities in AML and high expression of miR-191 and miR-199a were significantly correlated with poor prognosis [8]. In pediatric AML, there also have been some related studies about microRNAs, but it still remains limited. As shown in **Table 1**, we have summarized the microRNAs that play important roles in human pediatric AML. However, in both the diagnostic criteria and disease management, there are important differences between adults and children with AML [3]. So understanding the differences in microRNAs profiling between adults and pediatric AML will expand the potential of diagnostics and promote the identification of key microRNAs and genes, providing better insight into the leukemogenesis of pediatric AML. The aim of the present study was to identify important microRNAs and their regulated interaction network between adults and children with AML.

Material and methods

MicroRNA data and data analysis

The microRNA high-throughput dataset GSE35320 that contains AML samples from cell lines, bone marrow and pediatric patients and adult patients were download from Gene Expression Omnibus database [9]. In order to better compare the microRNAs expression between pediatric and adult patients, we just selected the chips that were all from bone marrow. In total, the processed expression data from 71 pediatric AML patient samples and 6 adulthood AML samples were used. The annotation information of the chips was available based on the GPL10993 platform. Differences between pediatric and children AML samples were calculated using Wilcox test and microRNAs with fold difference >1.5 and P<0.05 were considered statistically significant.

Prediction the target gens of the differentially expressed microRNAs

To obtain the target genes of the differentially expressed microRNAs, we employed a method [10] that integrates experimentally validated information from miRecords [11], TarBase [12], miR2Disease [13], and miRTarBase [14], and computational prediction results that were predicted at least two tools from HOCTAR [15], ExprTarget [16] and starBase [17].

Functional enrichment analysis

Gene ontology (GO) and KEGG pathway enrichment analysis of the target genes were performed using Database for Annotation, Visualization and Integrated Discovery (DAVID) [18]. The terms with Q-value (Benjamini) <0.01 were selected as highly significantly enriched.

Network construction and analysis

The Search Tool for the Retrieval of the Interacting Genes (STRING) [19], which provided both experimental and predicted interaction information, was used to search and construct the interaction network of the target genes of the differentially expressed microRNAs. The pairs with a combination score >0.7 were selected. Finally, the interaction network was analyzed and the degree of each node was calculated by Cytoscape. The core of the network was defined as the top 10 nodes whose degree is larger than the average degree in the network.

Results

Screening differentially expressed microRNAs

To identify the differentially expressed microRNAs between adults and children AML patients, publicly microarray datasets GSE35320 were obtained from GEO database. At a P<0.05 and |Fold Change|>1.5, a total of 7 microRNAs was considered to be differentially expressed between adults and children AML patient samples, including 5 upregulated and 2 downregulated microRNAs (**Table 2**). miR-16 and miR-

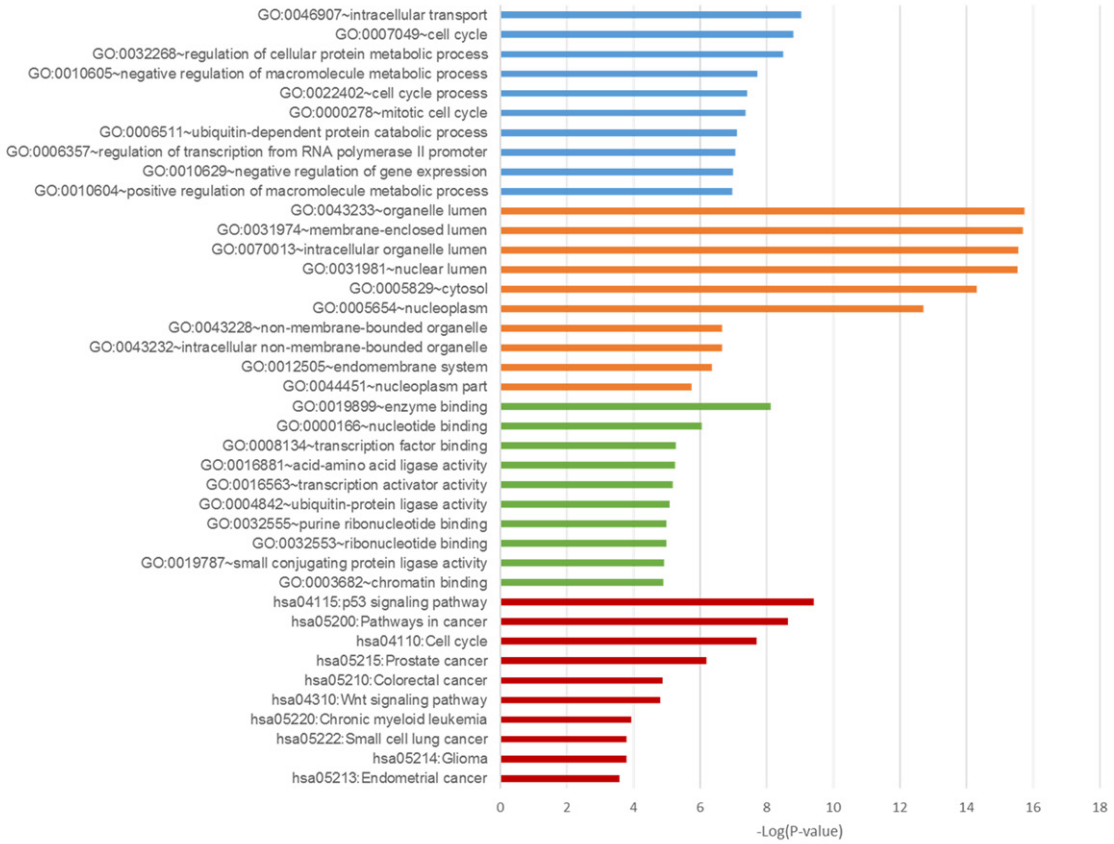

Figure 1. The Top 10 significant enriched DAVID terms in three GO domains and KEGG of target genes. Biological process, cellular component and molecular function terms are marked by blue, orange bars and green bars. KEGG pathways are marked by red bars.

142-5p exhibited the greatest upregulation and downregulation, separately.

Prediction target genes of differentially expressed microRNAs and functional enrichment analysis

The target genes of differentially expressed microRNAs were predicted by an integration method that was elaborated in the methods and materials. The number of target genes of each microRNA was shown in **Table 2**. miR-26b and miR-16 had the top two most predicted target genes. All the predicted target genes of the differentially expressed microRNAs were listed in Supplemental File 1.

To explore the function and annotation of the target genes, the GO that covers three domains: biological process, cellular component and molecular function and pathway enrichment analysis was performed by DAVID (**Figure 1** and Supplemental File 2). In biological process domain (blue bar), 87 terms were significantly enriched and many of them related regulation and cell cycle. There were 19 terms, many of which related with lumen and membrane, significantly enriched in cellular component. In molecular function domains, 21 terms were significantly enriched.

Additionally, 11 KEGG pathways were significantly enriched by the target genes of differentially expressed microRNAs. It is notable that all of the significantly enriched pathways were related with cancer and three of them directly with AML including p53 signaling pathway [20, 21], Wnt signaling pathway [22] and neurotrophin signaling pathway [23].

Construction and analysis of interaction network

The target genes of miR-142-5p and miR-16 were mapped to STRING database to screen

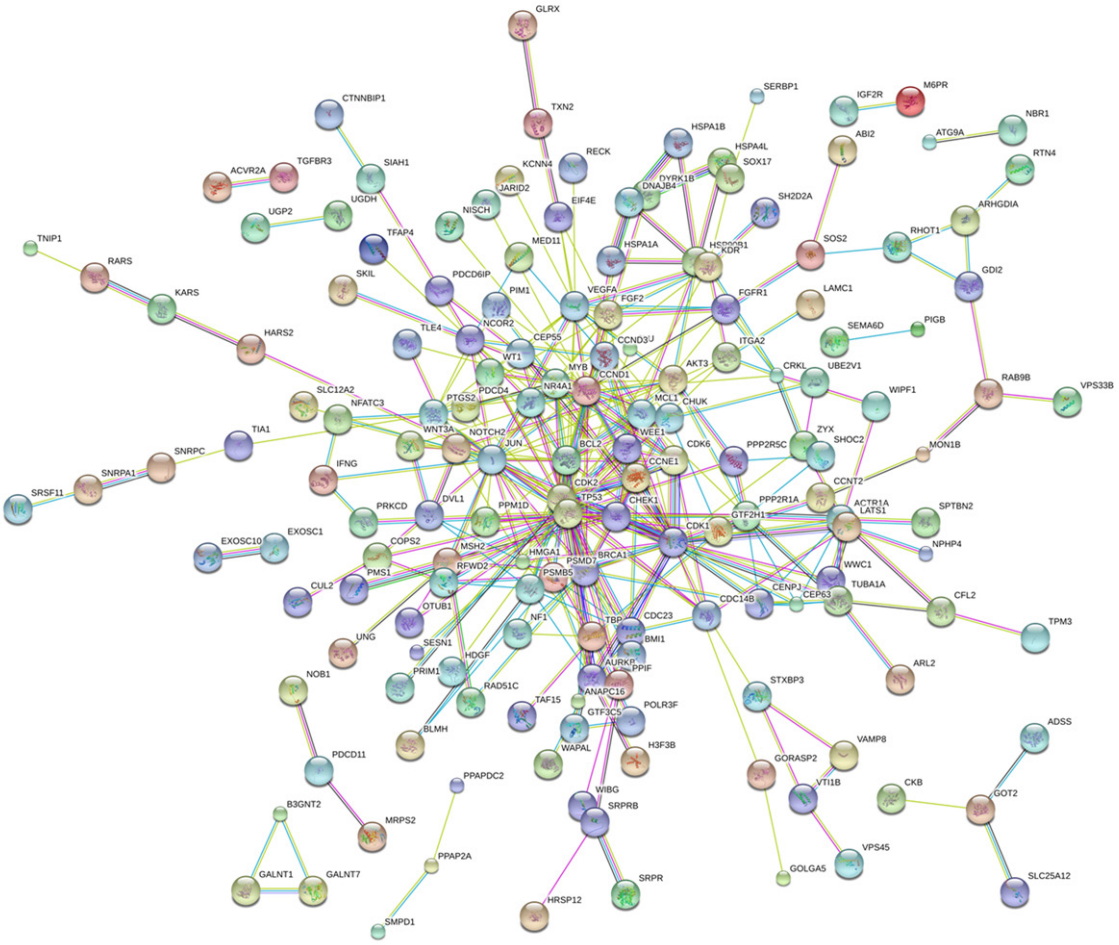

Figure 2. Interaction network of miR-16 target genes constructed by String.

significant interactions and construct their interaction networks. In the condition of combined score >0.7, there were no interactions among the target genes of miR-142-5p. Among 323 target genes of miR-16, 354 high confidence pairs of interactions were constructed as shown in **Figure 2** and Supplemental File 3. The top ten hub genes including TP53 (tumor protein p53), CDK1 (cyclin-dependent kinase 1), CCND1 (cyclin D1), JUN (jun proto-oncogene), CDK2 (cyclin-dependent kinase 2), BCL2 (B-cell CLL/lymphoma 2), VEGFA (vascular endothelial growth factor A), BRCA1 (breast cancer 1), MYB (v-myb myeloblastosis viral oncogene homolog) and FGF2 (fibroblast growth factor 2) constitute the core of the interaction network of miR-16 targets. Most of the core genes were related with cancer, suggesting the important role of miR-16 in pediatric AML.

Discussion

AML is one of the most common types of leukemia in children and the prognosis of pediatric AML is still poor. Therefore, there is an urgent requirement to investigate the mechanism of pediatric AML and to develop an effective preventative strategy specific for children. Recently, it has been demonstrated that microRNAs may represent molecular biomarkers for pediatric patients with AML [24, 25].

In the present study, the gene expression profile GSE35320 from GEO was used to analyze the differentially expressed microRNAs between adults and pediatric AML. As a result, seven microRNAs were obtained, as well as their target genes. Then the functional enrichment analysis was performed for the targets of selected microRNAs and quite a few of the significantly enriched biological processes were

related with cancer, especially three significantly enriched pathways directly play an important role in AML, which suggests that the differentially expressed microRNAs also have a role in pediatric AML.

Finally, the interaction networks of the miR-16 (most increased) and miR-142-5p (most decreased) target genes. Some of the core genes of the interaction network of miR-16 targets can be the biomarkers for pediatric AML. The high level protein expression of p53 can be a potential predictor of early relapse after hematopoietic stem cell transplantation in children with AML [21]. The expression BCL2 is an important prognostic feature to chemotherapy in denovo AML [26] and the relationships and relative levels with other proteins such as tyrosine kinase (FLT3) [27] can predict inferior outcome in pediatric AML. High levels of VEGFA correlated with overall survival [28] and it induced cell survival, proliferation, and protection against apoptosis via VEGFR signaling in pediatric AML [29, 30]. Although no interactions were detected among the target genes of miR-142-5p, the targets themselves were related with AML. For example, overexpression of ATP1B1 was associated with shorter overall survival (OS) and event-free survival of AML patients [31]. Patients with SF3B1 mutation presented with lower hemoglobin levels, increased platelet counts, and have shorter disease-free survival and overall survival than those without the mutation [32, 33]. These results demonstrated the potential roles of miR-16 and miR-142-5p and their targets in pathological mechanism of pediatric AML and can be potentially biomarkers for pediatric AML.

In conclusion, seven microRNAs were identified by comparing adults and children AML bone marrow samples and the targeted genes regulated by microRNAs indicated that they were correlated with p53 signaling pathway, Wnt signaling pathway and neurotrophin signaling pathway. miR-16 and miR-142-5p are likely to be presented as novel potential therapeutic targets and biomarkers for pediatric patients with AML. Further analyses and validation experiment are required to unravel the involvement pediatric AML development.

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Disclosure of conflict of interest

None.

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