Original Article

Systematic analysis reveals a lncRNA-miRNA-mRNA network associated with dasatinib resistance in chronic myeloid leukemia

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Background: Chronic myelogenous leukemia (CML) is a malignant tumor formed by the clonal proliferation of bone marrow hematopoietic stem cells. CML is a relatively rare disease, mainly affecting elderly patients, but the prevalence of CML is expected to increase dramatically. The tyrosine kinase inhibitors (TKIs) have changed the CML patients' treatment patterns and improved its treatment effect, but drug resistance still remains a significant problem to be solved. Therefore, the identification of biomarkers of CML resistance involved therein is essential for treatment and prognosis prediction.

Methods: Bioinformatics was used to analyze and construct a lncRNA-miRNA-mRNA network of CML resistance to dasatinib and predict key lncRNAs.

Results: By screening differentially expressed genes in CML resistant to dasatinib and comprehensively analyzing their functions and signal pathways, the core genes in these differential genes were found, and by predictive analysis of the upstream targets of these core genes. Finally, a network diagram containing lncRNA, miRNA, and mRNA was constructed.

Conclusions: MALAT1 as a lncRNA may be a tumor suppressor in patients with CML. According to our data, MALAT1 may have potential role as a molecular biomarker for the occurrence and development of CML resistance to dasatinib.

Keywords: Chronic myeloid leukemia; dasatinib resistance; lncRNA-miRNA-mRNA network; MALAT1

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Introduction

Chronic myelogenous leukemia (CML) is a malignant tumor formed by the clonal proliferation of bone marrow hematopoietic stem cells. There are 1–2 cases per 100,000 people, which accounts for about 15% of newly diagnosed leukemia cases in adults, and the incidence of CML increases annually (1). In the past 20 years, with the advent of imatinib [the first generation of tyrosine kinase inhibitors (TKIs)], TKIs have turned CML from fatal diseases into manageable chronic diseases (2). The majority of patients with CML who received BCR-ABL1 TKIs responded well (3). However, imatinib is far from perfect, with only approximately 60% of CML patients remaining

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on the standard daily dose of 400 mg after six years, either due to lack of drug tolerance or drug resistance. Among second-generation drugs, both dasatinib and nilotinib are more effective than imatinib, and they have been licensed in the United States. The emergence of TKIs in the treatment of CML opened a new era of precision medicine for various malignancies. In this era, relatively non-specific and toxic drugs were gradually replaced by safer and more tolerated drugs (4). Dasatinib is a second-generation TKI, with a longer-lasting intact hematological and cytogenetic response, as well as resistance to imatinib-resistant or intolerant CML. It is more potent and also shows advantages in newly diagnosed CML compared to imatinib (5). Although TKI has completely changed the CML patients' treatment patterns and greatly improved its treatment effect, drug resistance remains a significant problem to be solved (6). Therefore, studying the resistance mechanisms of CML and finding new targets for prevention and treatment are still hot topics in the field of cancer research.

Long non-coding RNA (lncRNA) is a non-protein transcript that ranges in length from 200 nucleotides (nt) to about 100 kilobases (kb) (7). While lncRNAs are post-transcriptionally modified in a way similar to mRNA, they are not translated into protein (8), but served key regulatory roles, such as mediating activity or localization of proteins, providing organizational scaffolds for subcellular structures, modulating transcriptional programs, and regulating miRNA expressions instead (9,10). Importantly, a large number of misregulated lncRNAs are involved in the occurrence and development of human cancers. These lncRNAs are involved in the regulation of cancer cell growth, metastasis, and chemotherapy drug resistance through a variety of mechanisms (11). An increasing number of studies report that dysregulation of lncRNA induces drug resistance in cancer cells (12). For example, NF-κB/HOTAIR promotes chemical resistance in ovarian cancer (13). Silencing linc-ROR can attenuate the expression of CD133+ cells in tumor-initiating cells, leading to the development of resistance to sorafenib in liver cancer cells (14). LncRNAs facilitate resistance to Ara-C treatment in AML (15). However, the potential role of lncRNAs in dasatinib resistance in chronic myeloid leukemia cells is unknown. It has been reported that the lncRNA MALAT1/miR-328 axis promotes CML cells' proliferation and imatinib resistance (16).

In our study, we followed the diagram in *Figure 1* and determined the expression profile of dasatinib resistance in CML cells through bioinformatics analysis, and aims to construct a lncRNA-miRNA-mRNA network for dasatinib resistance in CML cells. The key lncRNAs involved in drug resistance were revealed, which may pave the way for further research to identify clinical treatment targets or potential biomarkers of dasatinib resistance in chronic myeloid leukemia cells. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/apm-20-343).

Methods

Chip data

Gene expression data for both dasatinib-sensitive and dasatinib-resistant samples GSE33290 were downloaded from GEO (http://www.ncbi.nlm.nih.gov/geo/) (17). All raw data are standardized and log2 transformed. The differentially expressed genes were compared by GEO2R (https://ncbi.nlm.nih.gov/geo/geo2r/), comparing two or more samples in the GEO series. Differentiation expressed genes were identified according to $|\log2 \text{ (fold change)}| > 2$ and $P<0.05$.

Protein-protein interaction (PPI) network construction & hub-genes identification

A PPI network was set up by the STRING (v10.5) (https://string-db.org/) (18) and represented via Cytoscape 3.6.1. Then, we used 3 algorithms (Betweenness, Degree, Closeness) to analyze the overlapping genes with CytoHubba, which was employed to recognize highly interacted hub-genes (19).

Bioinformatic analysis

To explore the functional annotation and pathway enrichment, the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes database analyses were conducted using a Database for Annotation, Visualization and Integrated Discovery (DAVID: available online: http://david.abcc.ncifcrf.gov/) (20,21), FunRich (http://www.funrich.org/) (22) and STRING (https://string-db.org/).

Establishment of lncRNA-miRNA-mRNA network

Due to the complexity of mRNA-miRNA interactions, a single mRNA may predict a large number of miRNAs.

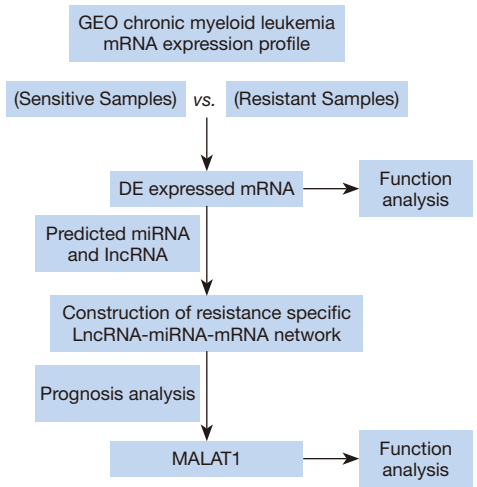

Figure 1 Flowchart of the analysis procedure.

Web-based tools mirDIP, miRDB, and miRanda were used to identify and predict miRNA functions, and plot the three sets of Wayne diagrams (http://bioinformatics.psb.ugent.be/webtools/Venn/). The obtained miRNAs were used to predict lncRNA in STARBASE and LncBase Predicted v.2. The network was visualized by Cytoscape3.6.1 software.

Survival analysis

Gene expression profiling interactive analysis (GEPIA) and OncoLnc (http://www.oncolnc.org/) are visualization webs server for analyzing the RNA sequencing expression data based on the TCGA (23). Overall survival was evaluated with the Kaplan-Meier method.

Statistical analysis

Data were expressed as the mean ± SD from at least three independent experiments for each group. All statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and P less than 0.05 was considered statistically significant.

Results

Expression profiles of mRNAs in chronic myeloid leukemia

The microarray dataset (GSE33290) that comprises mRNA expression profile in CML were analyzed. Thirty-nine mRNAs were significantly differentially expressed in dasatinib-resistant chronic myeloid leukemia patients compared with the dasatinib-sensitive CML patients in the GEO dataset. As a result, only 6 mRNAs were upregulated, whereas 33 mRNAs were downregulated on the criteria that |logFC| >2 and P<0.05. Sorted by |logFC| size, some high- and low-expressed gene names and corresponding information are shown in *Table 1*.

Recognition of hub genes from PPI network with CytoHubba

After introducing DEGenes into STRING, 28 isolated and non-interacting genes were removed, and the interactions among the overlapping genes was displayed in a PPI network in *Figure 2A*. The remaining 12 interacting genes were introduced into CYTOSCAPE for network visualization. The subnetwork was showed in *Figure 2B*, including 12 nodes and 25 edges were screened with CytoHubba, which revealed the vital roles of the twelve hub genes (*HLA-DQA1*, *MPL*, *BANK1*, *TCL1A*, *TNFRSF17*, *MZB1*, *IL7*, *CD19*, *IGJ*, *IGLL1*, *IGLL5*, *IGHV4-38-2*) in dasatinib resistance.

Functional enrichment of the twelve hub genes

Gene Ontology (GO) analysis in FunRich found that DEGenes focused on molecular function (MF) in receptor activity and receptor signaling complex scaffold activity in *Figure 3A*. *Figure 3B* demonstrated that these functions are closely related to immune response, signal transduction, and cell communication in biological processes (BP). The matching proteins and FDR were devoted to revealing the value of functional enrichment analysis. The enriched gene oncology terms and pathways were relevant with an adjusted FDR <0.05.

KEGG analysis of DEGenes in STRING demonstrated that these genes mainly interact with PI3K-Akt signaling pathway, Jak-STAT signaling pathway, and cytokine-cytokine receptor. According to the FDR <0.05 standard, the related enrichment pathways and their corresponding gene names were shown in *Table 2*.

LncRNA-miRNA-mRNA network construction

The miRDB database was used to predict a total of 1,666 corresponding miRNAs. The mirDIP database was used to predict a total of 76 corresponding miRNAs. In addition, 172 corresponding miRNAs were predicted by using miRanda. Then, we focused on delineating the

Table 1 Differentially expressed genes in GEO database

Gene symbol	Gene title	P value	logFC
RPS4Y2	Ribosomal protein S4, Y-linked 2	2.79E-02	3.842255
HLA-DQA1	Major histocompatibility complex, class II, DQ alpha 1	3.46E-02	2.474229
PRUNE2	Prune homolog 2	3.64E-03	2.319094
PTGDS	Prostaglandin D2 synthase	2.02E-04	2.272359
OCLN	Occludin	6.06E-10	2.229274
ID1	Inhibitor of DNA binding 1, HLH protein	2.57E-03	2.064524
CD22	CD22 molecule	1.90E-04	–2.00712
BANK1	B-cell scaffold protein with ankyrin repeats 1	7.35E-10	–2.01351
CFAP45	Cilia and flagella associated protein 45	1.99E-04	–2.03012
IL7	Interleukin 7	3.05E-06	–2.03998
KRT72	Keratin 72	8.51E-03	–2.13867
CD19	CD19 molecule	5.79E-06	–2.14802
CNTNAP2	Contact in associated protein-like 2	3.00E-05	–2.22341
KCNG1	Potassium voltage-gated channel modifier subfamily G member 1	8.90E-06	–2.24389
FCRL5	Fc receptor like 5	2.86E-05	–2.24615
SCFV	Single-chain Fv fragment	1.36E-07	–2.24879
MPL	MPL proto-oncogene, thrombopoietin receptor	1.62E-05	–2.29831
JCHAIN	Joining chain of multimeric IgA and IgM	4.08E-05	–2.32301
ALOX12	Arachidonate 12-lipoxygenase, 12S type	1.43E-05	–2.35115
IGLL5	Immunoglobulin lambda like polypeptide 5	4.39E-09	–2.51704
IGK	Immunoglobulin kappa locus	8.48E-09	–2.58176
MZB1	Marginal zone B and B1 cell specific protein	2.90E-08	–2.5952
IGLL1	Immunoglobulin lambda like polypeptide 1	3.16E-09	–2.60049
IGKV1-5	Immunoglobulin kappa variable 1-5	7.86E-08	–2.67078
IGHM	Immunoglobulin heavy constant mu	9.02E-09	–2.69825
IGH	Immunoglobulin heavy locus	4.80E-06	–2.70581
IGHG4	Immunoglobulin heavy constant gamma 4 (G4m marker)	1.72E-07	–2.76976
LOC102723407	Putative V-set and immunoglobulin domain-containing-like protein IGHV4OR15-8	1.89E-08	–2.77353
SKAP2	Src kinase associated phosphoprotein 2	1.89E-08	–2.77353
TCL1A	T-cell leukemia/lymphoma 1A	2.65E-06	–2.94444
TNFRSF17	TNF receptor superfamily member 17	1.20E-06	–3.10431

dasatinib resistance-specific mRNA-miRNA correlation relationship. The dasatinib resistance-specific mRNA-miRNA correlation network contained 12 mRNAs, 172 miRNAs predicted in miRanda and 135 mRNA-miRNA correlation edges in *Figure 4A*. Based on the above results, the network diagram constructed in the CYTOSCAPE

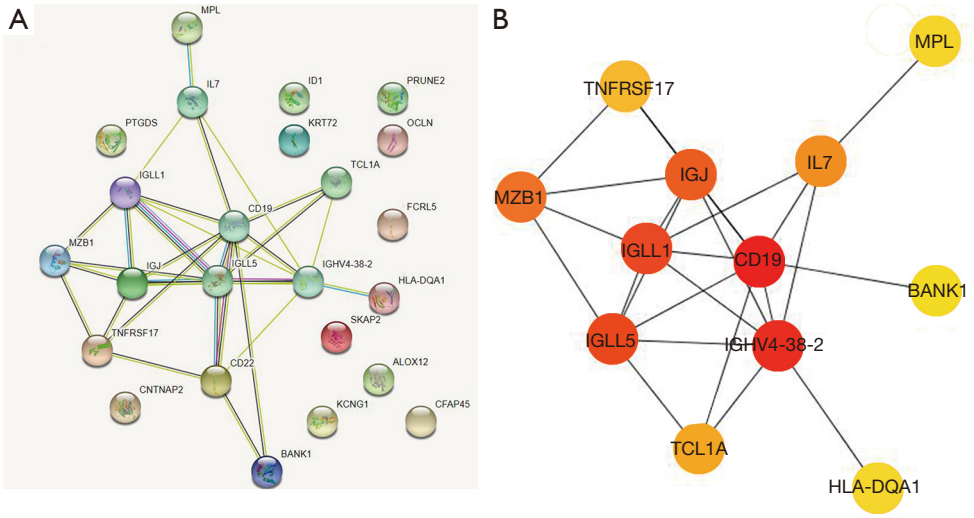

Figure 2 Interactions among the overlapping genes in a PPI network and recognition of hub genes from PPI network with CytoHubba. (A) The 12 overlapping genes were imported to search by names in STRING database. (B) The current PPI network was visualized by Cytoscape 3.6.1. The network contains 12 nodes and 25 edges. PPI, protein-protein interaction.

for the predicted lncRNA, miRNAs and mRNAs. The network contains 15 nodes (7 lncRNAs, 3 miRNAs, 5 mRNAs) and 14 relationship pairs. *Figure 4B* summarized the network including seven lncRNAs (MALAT1, OIP5-AS1, LINC00665, LINC00657, ERVK3-1, NEAT1, CTC-444N24.11), three miRNAs (hsa-miR-28-5p, hsa-miR-129-5p, hsa-miR-543) and five mRNAs (MPL, IL7, IGJ, HLA-DQA1, BANK1) which were generated by Cytoscape 3.6.1.

Three overlapping miRNAs that might play critical roles in dasatinib-resistance were selected by intersecting the predicted miRNAs (*Figure 5*). These 3 miRNAs were used to predict the upstream lncRNA in STARBASE and LncBase Predicted v.2. According to the screening criteria, 7 lncRNAs were predicted.

Key RNAs and their associated clinical features

In order to identify the specific RNAs with prognostic characteristics, RNAs were chosen according to the bioinformatics analysis and the LncRNA-miRNA-mRNA network were analyzed the effects significant for survival ($P<0.05$) through analysis of the association between key RNAs and CML patients' survival periods.

Among the differentially expressed RNAs, one mRNA (IL7), one miRNA (hsa-miR-28-5p), and one lncRNA (MALAT1) were found to be associated with the overall survival of patients with CML by prognosis analysis. Kaplan-Meier survival curves indicated that the lncRNA MALAT1 (*Figure 6A*) positively correlated with overall survival, whereas IL7 (*Figure 6B*) and hsa-miR-28-5p (*Figure 6C*) were negatively associated with overall survival.

Characteristics of MALAT1 in CML

According to GO analysis, anomalous expression of MALAT1 is related to aberrant regulation of gene function groups such as regulation of alternative mRNA splicing, protein binding, and protein complex binding in *Figure 7A*.

Protein–protein interaction analysis revealed that metastasis associated lung adenocarcinoma transcript 1 (non-protein coding) (MALAT1) can interact with several proteins including A-kinase anchoring protein 9 (AKAP9), splicing factor proline and glutamine rich (SFPQ), serine and arginine rich splicing factor 1 (SRSF1), ELAV like RNA binding protein 1 (ELAVL1), tumor protein p53 (TP53), enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), SUZ12 polycomb repressive complex 2 subunit(SUZ12), Sp1 transcription factor (SP1), cadherin 1(CDH1), zinc finger E-box binding homeobox 1 (ZEB1) in *Figure 7B*. KEGG analysis of MALAT1 in STRING revealed that it mainly interacts with IL-17 signaling pathway, transcriptional misregulation in cancer and endocrine resistance are closely related. According to the FDR<0.05 standard, the related enrichment pathways and their corresponding gene names are shown in *Table 3*.

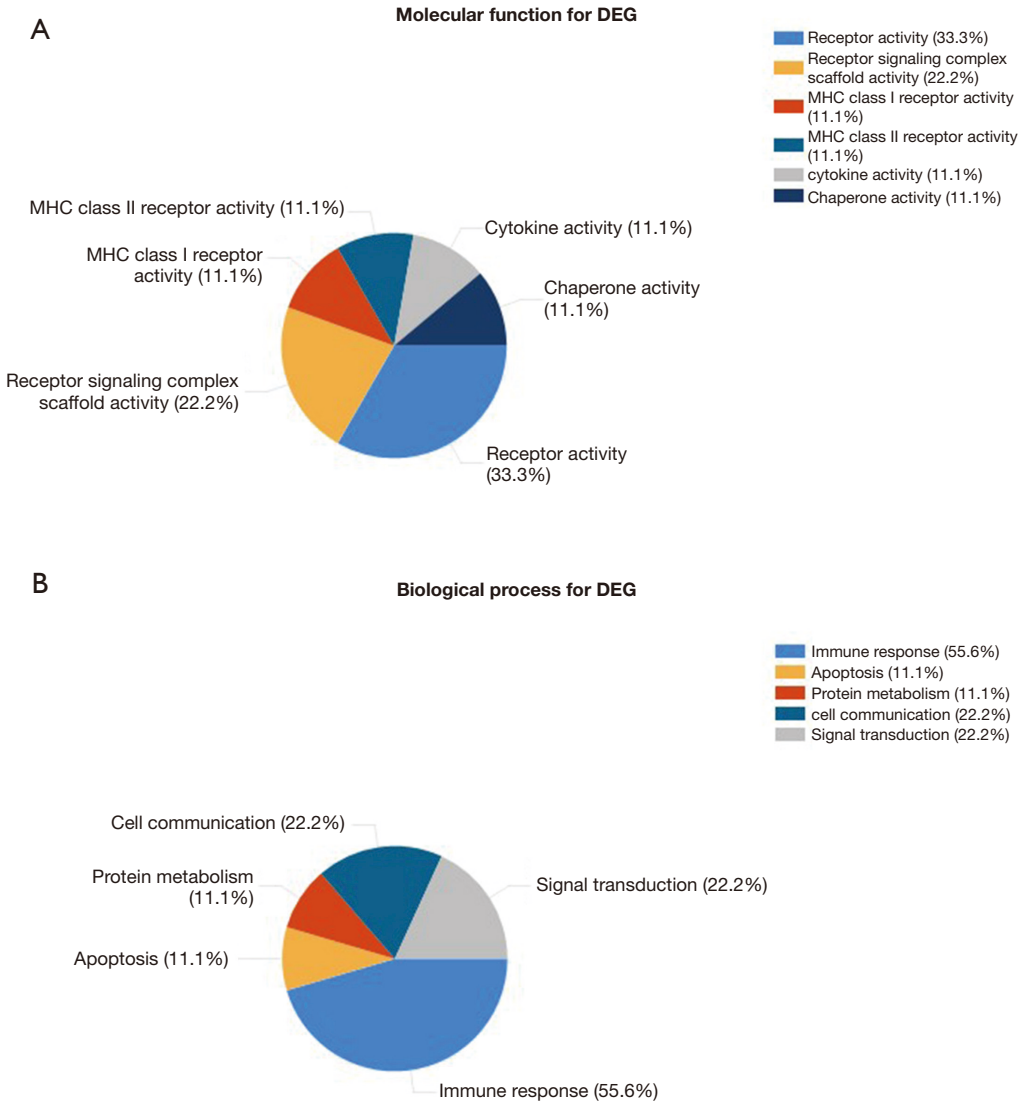

Figure 3 KEGG and GO analysis results of the twelve hub genes. The enrichment annotations of the seven hub genes: molecular function (A) and biological process (B). GO, Gene Ontology.

Discussion

CML is a relatively rare disease (5,980 new cases each year in the United States), mainly affecting elder patients (median age at diagnosis of 67 years), but the prevalence of CML is expected to increase dramatically. The effectiveness of TKI treatment and reduction in CML-related deaths is obvious (24). Therefore, the identification of biomarkers of CML resistance involved therein is essential for treatment and prognosis prediction.

In the GEO database, dasatinib-resistant CML sample information was used to screen 39 differentially expressed genes with high reliability, and 12 core genes were found. In this study, miRDIP, miRDB and miRanda were used to predict the upstream miRNAs of 12 core genes. Three miRNAs (hsa-miR-28-5p, hsa-miR-129-5p, hsa-miR-543) were found through the intersection analysis. Studies have shown that these miRNAs are closely related to leukemia development. For example, the decrease in miR-28-5p endogenous levels by dexamethasone counteract their ability to block NDRG2's stress response increase to dexamethasone (25); miR-28-5p reinforce the notion that inactivation of targeted genes is linked to malignant progression in cancer (26). These results suggested that

Table 2 Pathways enrichments analysis of 12 hub genes from STRING

Term ID	Term description	FDR	Matching proteins in network
hsa04640	Hematopoietic cell lineage	1.16E-05	CD19, HLA-DQA1, IGHV4-38-2, IL7
hsa05340	Primary immunodeficiency	3.52E-05	CD19, IGHV4-38-2, IGLL1
hsa04672	Intestinal immune network for IgA production	3.84E-05	HLA-DQA1, IGHV4-38-2, TNFRSF17
hsa04151	PI3K-Akt signaling pathway	0.00047	CD19, IGHV4-38-2, IL7, TCL1A
hsa05310	Asthma	0.0012	HLA-DQA1, IGHV4-38-2
hsa05169	Epstein-Barr virus infection	0.0014	CD19, HLA-DQA1, IGHV4-38-2
hsa05330	Allograft rejection	0.0014	HLA-DQA1, IGHV4-38-2
hsa04060	Cytokine-cytokine receptor interaction	0.0022	IL7, MPL, TNFRSF17
hsa05150	Staphylococcus aureus infection	0.0022	HLA-DQA1, IGHV4-38-2
hsa05320	Autoimmune thyroid disease	0.0022	HLA-DQA1, IGHV4-38-2
hsa05416	Viral myocarditis	0.0022	HLA-DQA1, IGHV4-38-2
hsa04662	B cell receptor signaling pathway	0.0029	CD19, IGHV4-38-2
hsa05140	Leishmaniasis	0.0029	HLA-DQA1, IGHV4-38-2
hsa05323	Rheumatoid arthritis	0.0036	HLA-DQA1, IGHV4-38-2
hsa05322	Systemic lupus erythematosus	0.0042	HLA-DQA1, IGHV4-38-2
hsa04145	Phagosome	0.009	HLA-DQA1, IGHV4-38-2
hsa04630	Jak-STAT signaling pathway	0.0103	IL7, MPL
hsa05152	Tuberculosis	0.0111	HLA-DQA1, IGHV4-38-2

FDR, false discovery rate.

the predicted miRNAs might play an important role in promoting leukemia occurrence or progression.

Using STARBASE and LncBase Predicted v.2 software to predict the upstream lncRNAs of these 3 miRNAs, a total of 7 lncRNAs were screened (MALAT1, OIP5-AS1, LINC00665, LINC00657, ERVK3-1, NEAT1, CTC-444N24.11). Studies have shown that some of these lncRNAs are closely related to drug resistance. For example, LncRNA MALAT1 promotes cell proliferation and imatinib resistance by sponging miR-328 in CML. Lots of evidences were confirmed that MALAT1 related to drug resistance (27-29) and cancer development (30). These results indicate that the predicted lncRNAs play an important role in drug resistance in leukemia.

The GO analysis results showed that the 12 hub genes were obtained focused on the molecular functions of the receptor activity and the receptor signaling complex scaffold activity as well as MHC class 1 receptor activity, MHC class 2 receptor activity, cytokine activity, and chaperone activity. These functions are closely related to immune response, signal transduction and cellular communication, as well as protein metabolism and apoptosis. In addition, KEGG analysis showed that these genes are mainly related to the hematopoietic cell lineage, primary immune deficiency, asthma, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, allograft rejection, and also related to PI3K-Akt Signaling pathway, Jak-STAT signaling pathway, B cell receptor signaling pathway, the interaction of cytokines and cytokine receptors, as well as the intestinal immune network that produces IgA, phagosomes; Epstein-Barr virus infection, Staphylococcus aureus infection, Viral myocarditis, leishmaniasis, tuberculosis. These pathways predicted above are related to metabolism, apoptosis, immunity and transcription regulation, which may be related to the potential regulatory functions of CML.

Through systematic analysis, the dasatinib-resistant lncRNA-miRNA-mRNA network of CML were revealed. We also found that the lncRNAs involved in dasatinib resistance primarily regulate metabolic pathways and the key lncRNA MALAT1 was related to the positive prognosis

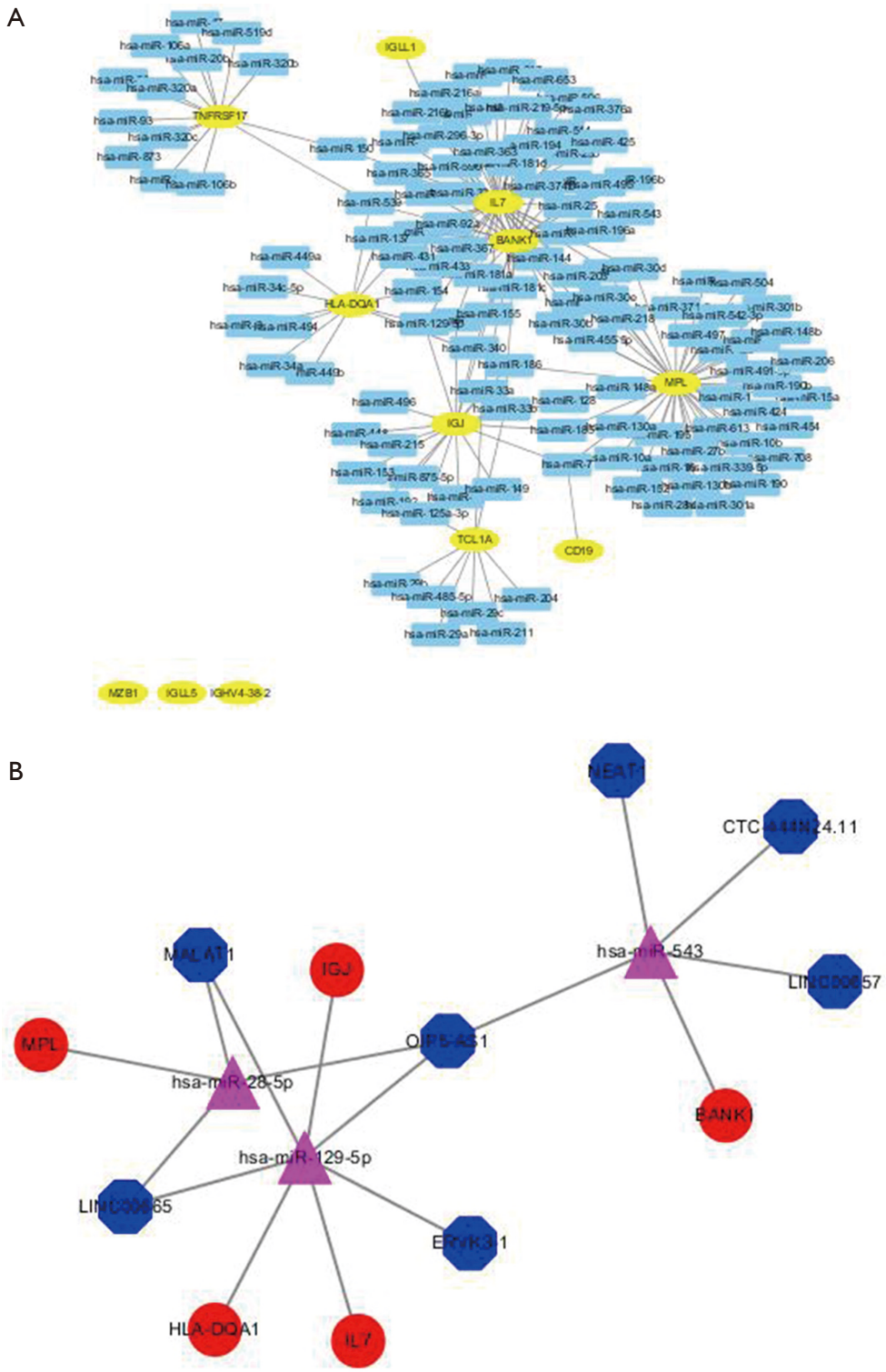

Figure 4 Dasatinib resistance-specific mRNA-miRNA correlation network and LncRNA-miRNA-mRNA network. (A) The rectangle and oval represent miRNA and mRNA, respectively. (B) The network contains 15 nodes (7 lncRNAs, 3 miRNAs, 5 mRNAs) and 14 relationship pairs was generated by Cytoscape 3.6.1.

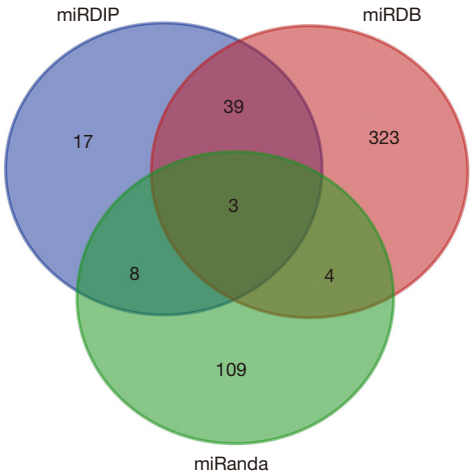

Figure 5 Venn diagram of predicted miRNAs in miRDB, mirDIP and miRanda database. The miRDB database predicted a total of 1,666 corresponding miRNAs and the mirDIP database predicted a total of 76 corresponding miRNAs. In addition, 172 corresponding miRNAs were predicted through miRanda. Venn map of miRNA from miRDB, mirDIP and miRanda.

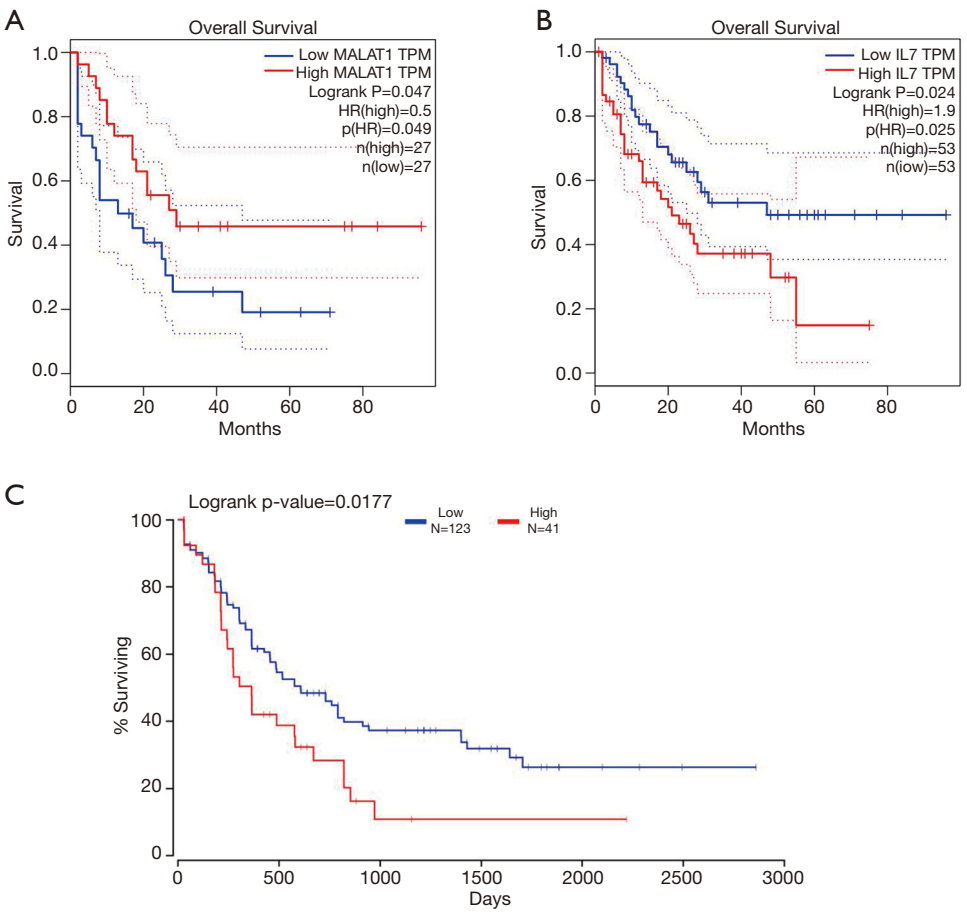

Figure 6 Kaplan-Meier survival analysis in CML patients in TCGA datasets. (A) MALAT1 positively correlated with overall survival; (B) IL7 was negatively associated with overall survival; (C) hsa-miR-28-5p was negatively associated with overall survival. CML, chronic myelogenous leukemia.

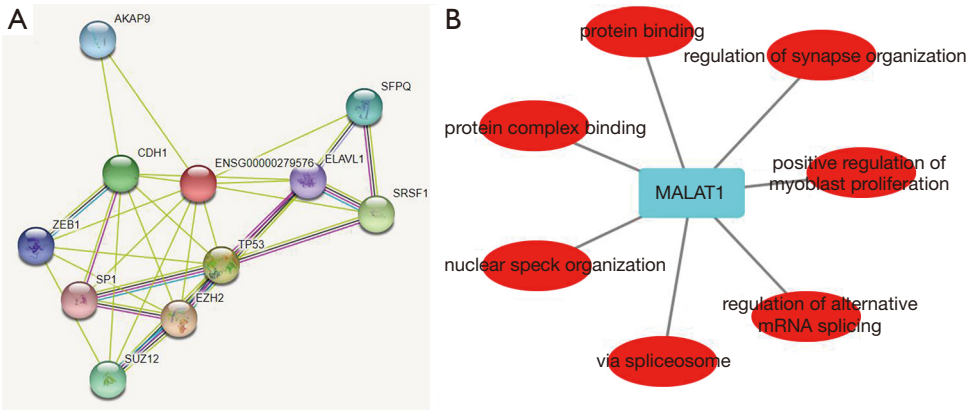

Figure 7 Characteristics of MALAT1 in CML. (A) Protein-protein interaction analysis of MALAT1; (B) GO analysis showed anomalous expression of MALAT1 was related to aberrant regulation of gene function groups such as regulation of alternative mRNA splicing, protein binding, and protein complex binding. CML, chronic myelogenous leukemia; GO, Gene Ontology.

Table 3 Pathways enrichments analysis of lncRNA MALAT1

Term ID	Term description	FDR	Matching proteins in network
hsa05202	Transcriptional misregulation in cancer	0.0046	SP1, TP53, ZEB1
hsa05206	MicroRNAs in cancer	0.0046	EZH2, TP53, ZEB1
hsa05216	Thyroid cancer	0.0046	CDH1, TP53
hsa05219	Bladder cancer	0.0046	CDH1, TP53
hsa04137	Mitophagy - animal	0.0063	SP1, TP53
hsa05213	Endometrial cancer	0.0063	CDH1, TP53
hsa05218	Melanoma	0.0068	CDH1, TP53
hsa01522	Endocrine resistance	0.0096	SP1, TP53
hsa04657	IL-17 signaling pathway	0.0096	ELAVL1, SRSF1
hsa05215	Prostate cancer	0.0096	TP53, ZEB1
hsa05200	Pathways in cancer	0.0149	CDH1, SP1, TP53
hsa05224	Breast cancer	0.0159	SP1, TP53
hsa05226	Gastric cancer	0.0159	CDH1, TP53
hsa05168	Herpes simplex infection	0.0203	SRSF1, TP53
hsa05016	Huntington's disease	0.0215	SP1, TP53

FDR, false discovery rate.

of CML. The expressions of IL7 and hsa-miR-28-5p were negatively correlated with the overall survival of patients. Nevertheless, there are no reports on the association of MALAT1 with dasatinib-resistance in CML. In addition, other lncRNAs that involved in dasatinib resistance of CML cells were deserved detailed analysis in the future.

Conclusions

All in all, we predict that MALAT1 as a lncRNA may be a tumor suppressor for CML patients. According to our data, MALAT1 may have potential as a molecular biomarker for the occurrence and development of CML resistance. Whether it can be effective therapeutic targets for changing

the prognosis of tolerating dasatinib in CML patients is worth further exploration.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-343). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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