Genetic Chinese Medicine Network Pharmacology Research, Quercetin Improves Drug Resistance in Acute Myeloid Leukemia by Targeting *CXCL10*

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Research

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Abstract

Background: Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is a highly heterogeneous and fatal disease. At present, the main method of treatment of AML is chemotherapy, but patients who relapse often develop resistance and are not sensitive to chemotherapy. Chinese medicine network pharmacology can provide new ideas about improving AML resistance.

Methods: The gene expression data of relapsed drug-resistant AML and primary AML are from Gene Expression Omnibus (GEO) database. Based on the network pharmacology of traditional Chinese medicine, the effective components and target genes of Jiedu Huayu Decoction were analyzed. we performed Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Ontology (GO) analyses, Protein-protein interaction (PPI) network and construction on overlapping genes. We will perform prognostic analysis and gene correlation analysis of overlapping genes in GEPIA. The binding energy between the differential gene and the active ingredient of the drug was studied by molecular docking.

Results: We found that quercetin, the active ingredient in Jiedu Huayu Decoction, can target *CXCL 10*, thereby improving AML resistance.

Conclusions: In this study, we found that quercetin improves drug resistance in acute myeloid leukemia by targeting *CXCL 10* based on the GEO database and the network pharmacology study of Chinese medicine.

Introduction

Acute myeloid leukemia (Acute myeloid leukemia, AML) is a type of malignant hematological disease characterized by rapid progression of the disease and poor prognosis[1]. According to the latest cancer statistics in 2020, there have been 11,180 deaths and 19,940 new cases of AML[2]. With the improvement of chemotherapy regimens, hematopoietic stem cell transplantation, gene targeted therapy, biological immunotherapy, traditional Chinese medicine and other treatment methods, some progress has been made in the treatment of AML. However, due to severe side effects and multi-drug resistance, about two-thirds of the patients are prone to relapse after first-line treatment[3, 4]. After recurrence, chemotherapy has poor effect and poor prognosis, and there is no good treatment plan for the patients after recurrence[5, 6]. Once AML patients relapse, the tumor cells are easy to develop resistance to chemotherapeutic drugs, and it is easy to develop multi-drug resistance to a variety of chemotherapeutic drugs with different structures and functions, and then it is difficult to cure[7–9]. Therefore, there is an urgent need to develop new drugs to improve AML resistance.

Traditional Chinese Medicine (TCM) has been used in Asia for more than 2,000 years. Due to its outstanding efficacy, abundant resources and low toxicity, it has gradually been accepted by non-Chinese medicine practitioners. In the clinical treatment of cancer, many traditional Chinese medicine formulations are used alone or as adjuvants for conventional chemotherapy[10, 11]. Studies have shown that Chinese medicine combined with chemotherapy can increase the remission rate of AML patients and

improve the resistance of AML patients[12, 13]. The jiedu huayu recipe medicine is composed of Indigo Naturalis, Pseudobulbus Cremastrae Seu Pleiones, Paris polyphylla, Polygonum cuspidatum, Curcuma Zedoaria, Ligusticum chuanxiong Hort, Salvia Miltiorrhiza and Psoraleae Fructus. Studies have shown that this prescription has an important effect on improving drug resistance in leukemia patients[14]. In traditional Chinese medicine formulations, a variety of herbal ingredients and biologically active ingredients target multiple receptors and produce synergistic or antagonistic effects[15]. However, its drug components are numerous and drug interactions are complex, which brings certain difficulties to the mechanism of its anti-tumor effect. Chinese medicine network pharmacology is a new research field that combines pharmacology and pharmacodynamics. It is based on systems biology, multi-directional pharmacology and high-throughput analysis, analyzes the connection between drugs, targets and diseases by building a biological network, and has been widely used in Chinese medicine to treat cancer[16, 17]. Analyzing the ingredients of Jiedu Huayu Recipe through network pharmacology, we discovered a hydroxyflavonoid called quercetin, which is the active ingredient of Polygonum cuspidatum and its chemical name is 3,3,4,5,7 -Pentahydroxyflavone[18]. Anti-inflammatory, antioxidant and anticancer activities are some of the mainly described quercetin mechanisms of action[19–21]. And it has been found that quercetin can improve the remission rate of AML chemotherapy and induce apoptosis of HL60 cells[22, 23]. Studies have found that quercetin can improve the drug resistance of prostate cancer, breast cancer, gastric cancer and other cancers[24–26], but its mechanism of improving drug resistance in AML is less.

In this study, we searched for the bioactive ingredients and targets of the drug through the network pharmacology of traditional Chinese medicine and the GEO database to screen AML relapsed resistance genes, and finally found that quercetin targets *CXCL10* and cooperates with *HMOX1* and *IRF1* improve AML resistance.

Materials And Methods

Microarray data

We extracted gene expression (GSE66525) profiling data from the Gene Expression Omnibus (GEO) database at the National Center for Biotechnology Information. The AML-associated dataset GSE66525 submitted by Wieser R based on the GPL11532 platform was obtained from the GEO database and includes 11 AML primary samples and 11 AML recurrence normal samples.

Identification of differentially expressed genes (DEGs)

The limma package is a core component of Bioconductor, an R-based open-source software development project in statistical genomics[27]. The package is designed in such a way that, after initial pre-processing and normalization, the same analysis pipeline is used for data from all technologies. For the data from GEO, the R package limma was applied to perform analysis to identify the DEGs. The “R” software was applied to construct heat maps and Volcano map, and the regions in which the differential genes were mainly concentrated were highlighted.

Identification of Biologically active ingredients in jiedu huayu recipe

All components of the eight Chinese medicinal herbs in jiedu huayu recipe (Indigo Naturalis, Pseudobulbus Cremastrae Seu Pleiones, Paris polyphylla, Polygonum cuspidatum, Curcuma Zedoaria, Ligusticum chuanxiong Hort, Salvia Miltiorrhiza and Psoraleae Fructus) were retrieved from the traditional Chinese medicine systems pharmacology (TCMSP) database (<http://tcmospw.com/>)[28]. In drug absorption, distribution, metabolism, and excretion (ADME) processes, oral bioavailability (OB) is one of the most significant pharmacokinetic parameters[29]. As a qualitative concept applied in drug design to estimate the druggability of a molecule[30], the drug-likeness (DL) index is useful for rapid screening of active substances. The active components were filtered by combining oral bioavailability (OB) $\geq 30\%$ and drug-likeness (DL) index ≥ 0.18 as suggested by the TCMSP database.

Prediction of Drug Targets for Biologically active ingredients in jiedu huayu recipe

The protein targets of the active substances in jiedu huayu recipe were retrieved from the TCMSP database and the traditional Chinese medicine integrated database (TCMID, <http://www.megabionet.org/tcmid/>).

Screening of overlapping genes between DEGs and drug targets of biologically active ingredients

The target gene of the active ingredient of the drug and the differential gene in the GEO database are analyzed by Perl software, and the overlapping part of the two differential genes is defined as a common differential gene, and its expression level in the GEO database is stored for subsequent analysis.

Functional enrichment analyses for overlapping genes

The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a database resource for understanding high-level functions and utilities of the biological system from molecular-level information. The Gene Ontology (GO) could be used to perform enrichment analysis. We used DAVID (<https://david.ncifcrf.gov/>) to make KEGG pathway analysis and GO enrichment analysis.

Protein–protein interaction (PPI) network construction

PPI analysis is used to search core genes and gene modules related to carcinogenesis. In this study, PPI network analysis of the overlapping genes were performed using the search tool for the Retrieval of Interacting Genes (STRING) database.

Prognostic Analysis and Gene Correlation Analysis in GEPIA

Gene Expression Profiling Interactive Analysis (GEPIA), a web-based tool to deliver fast and customizable functionalities based on TCGA and GTEx data, provides key interactive and customizable functions including differential expression analysis, profiling plotting, correlation analysis, patient survival analysis, similar gene detection and dimensionality reduction analysis[31]. We used GEPIA to analyze the prognosis of 17 overlapping genes. P-values < 0.05 were considered statistically significant. Then we used

prognostic-related genes and 17 overlapping genes for genetic correlation analysis. The correlation of gene expression was evaluated by Spearman's correlation and statistical significance, and the strength of the correlation was determined using $R \geq 0.5$.

Molecular docking

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design[32]. We use molecular docking to predict the combination of active ingredients of drugs and differential genes. First of all, we prepared 3D structure of targets and compounds which were mined from Protein Data Bank (PDB) (<https://www.rcsb.org/>) and PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) databases[33, 34]. Then, the AutoDock tool was applied to perform a molecular docking[35]. Finally, PyMOL 2.3.2 software was used for visual processing to check the binding status of ligands and receptor binding sites[36].

Results

Identification of differentially expressed genes in primary and relapsed AML patients

For the AML-associated dataset GSE66525 from GEO, the R package limma was applied to perform analysis to identify the DEGs. We screened a total of 458 differential genes, of which 133 genes were up-regulated in patients with relapsed AML, and 326 genes were down-regulated in patients with recurrent AML. Heat map and volcano map show differential gene expression (Fig. 1A, 1B).

Network pharmacological analysis of Chinese medicine effective ingredients and targets of Jiedu Huayu Recipe

We first screened the effective ingredients of eight Chinese herbal medicines (Indigo Naturalis, Pseudobulbus Cremastrae Seu Pleiones, Paris polyphylla, Polygonum cuspidatum, Curcuma Zedoaria, Ligusticum chuanxiong Hort, Salvia Miltiorrhiza and Psoraleae Fructus) in the Jiedu Huayu Recipe in the TCMSP database by setting the conditions of $OB \geq 30\%$ and $DL \geq 0.18$, and then searched for the target genes corresponding to each active ingredient. We found the active ingredients of six kinds of traditional Chinese medicines in the TCMSP database, but did not find the active ingredients of Paris polyphylla and Psoraleae Fructus. When searching for the target genes of the active ingredients, we found five of the target genes of traditional Chinese medicine, but did not find the target of the active ingredients of Pseudobulbus Cremastrae Seu Pleiones. We organize the drugs, active ingredients, and target genes into Table 1.

Table 1

Drug active ingredients and target genes corresponding to the prescription drugs in Jiedu Huayu Recipe.

Drug	Active ingredients	Target gene
Salvia Miltiorrhiza	MOL007101	<i>NCOA2</i>
	MOL007088	<i>NCOA2</i>
	MOL007093	<i>PPARG, NCOA2</i>
	MOL007064	<i>NCOA2</i>
	MOL007049	<i>PPARG, NCOA2</i>
	MOL007122	<i>NCOA2</i>
	MOL007098	<i>NCOA2</i>
	MOL007041	<i>PPARG, NCOA2</i>
	MOL007143	<i>NCOA2</i>
	MOL007119	<i>NCOA2</i>
	MOL007036	<i>NCOA2</i>
	MOL007108	<i>NCOA2</i>
	MOL007115	<i>NCOA2</i>
	MOL002651	<i>PPARG</i>
	MOL007125	<i>PPARG, NCOA2</i>
	MOL007132	<i>PPARG</i>
	MOL007100	<i>PPARG</i>
	MOL007050	<i>PPARG</i>
	MOL007154	<i>CASP3</i>
	MOL001771	<i>NCOA2</i>
	MOL007120	<i>NCOA2</i>
	MOL001601	<i>NCOA2</i>
	MOL007156	<i>PPARG, NCOA2</i>
	MOL000006	<i>NCOA2, MMP2, CASP3, PPARG, HMOX1, IFNGR1, PTGES</i>
	MOL000358	<i>NCOA2, CASP3, PRKCA</i>

Drug	Active ingredients	Target gene
Ligusticum Chuanxiong Hort	MOL002157	<i>NCOA2</i>
	MOL002135	<i>PPARG</i>
	MOL001494	<i>NCOA2</i>
	MOL000359	<i>NCOA2</i>
	MOL000006	<i>NCOA2, MMP2, CASP3, PPARG, HMOX1, IFNGR1, PTGES</i>
	MOL000358	<i>NCOA2, CASP3, PRKCA</i>
Indigo Naturalis	MOL002309	<i>PPARG</i>
	MOL000006	<i>NCOA2, MMP2, CASP3, PPARG, HMOX1, IFNGR1, PTGES</i>
	MOL000358	<i>NCOA2, CASP3, PRKCA</i>
Polygonum Cuspidatum	MOL002268	<i>NCOA2</i>
	MOL000492	<i>NCOA2</i>
	MOL000098 (Quercetin)	<i>PPARG, NCOA2, MMP2, CASP3, PRKCA, HMOX1, CAV1, CYP1B1, SERPINE1, IFNGR1, NCF1, PPARG, CXCL10, SPP1, ACP, IRF1</i>
	MOL000006	<i>NCOA2, MMP2, CASP3, PPARG, HMOX1, IFNGR1, PTGES</i>
	MOL000358	<i>NCOA2, CASP3, PRKCA</i>
Curcuma Zedoaria	MOL000296	<i>NCOA2</i>
	MOL000006	<i>NCOA2, MMP2, CASP3, PPARG, HMOX1, IFNGR1, PTGES</i>
	MOL000358	<i>NCOA2, CASP3, PRKCA</i>

Screening and analysis of overlapping genes between DEGs and bioactive ingredient drug targets

We use Perl software to analyze the overlapping genes of the target gene of the active ingredient of the drug and the differential gene in the GEO database. We screened 17 overlapping genes. Compared with primary patients with AML, the expression levels of overlapping genes in relapsed patients are sorted into Table 2. And we show the active ingredients of drugs corresponding to overlapping genes (Fig. 2A). We found that the 17 overlapping genes screened were basically consistent with the target genes of

quercetin, the active ingredient of *Polygonum cuspidatum* (Table 3, Fig. 2B). We speculate that quercetin has a certain therapeutic effect on patients with relapsed resistant AML.

Table 2
The overlapping genes of the target gene of the active ingredient of the drug and the differential gene in the GEO database.

Genes	logFC	p value
<i>NCOA2</i>	-0.71039374	0.019247061
<i>PPARG</i>	-0.824038153	0.048075407
<i>MMP2</i>	1.763107463	0.014933989
<i>CASP3</i>	0.830909926	0.010240489
<i>HMOX1</i>	-1.524949264	0.010362237
<i>IFNGR1</i>	-0.639788165	0.020564584
<i>PTGES</i>	-0.680890169	0.001482936
<i>PRKCA</i>	-1.240566198	0.037672849
<i>CAV1</i>	1.997562161	0.007925876
<i>CYP1B1</i>	-1.981788198	0.007133341
<i>SERPINE1</i>	1.216215851	0.004921618
<i>NCF1</i>	-1.719297665	0.008906454
<i>PPARD</i>	-0.75128786	0.017145662
<i>CXCL 10</i>	-1.771414628	0.006680325
<i>SPP1</i>	1.223800376	0.032785076
<i>ACPP</i>	-1.413469603	0.000649293
<i>IRF1</i>	-0.722719669	0.000622327

Table 3

Classification	Genes
MOL000098 (Quercetin)	<i>PPARG, NCOA2, MMP2, CASP3, PRKCA, HMOX1, CAV1, CYP1B1, SERPINE1, IFNGR1, NCF1, PPARD, CXCL 10, SPP1, ACPP, IRF1</i>
Overlapping genes	<i>PPARG, NCOA2, MMP2, CASP3, PRKCA, HMOX1, CAV1, CYP1B1, SERPINE1, IFNGR1, NCF1, PPARD, CXCL 10, SPP1, ACPP, IRF1, PTGES</i>

Then, we constructed a PPI network with 17 overlapping genes, and performed KEGG pathway analysis (Fig. 2C, 2D). KEGG pathway analysis found that overlapping genes are mainly enriched in AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, Fluid shear stress and atherosclerosis, Influenza A, Proteoglycans in cancer, MicroRNAs in cancer, TNF signaling pathway, Leukocyte transendothelial migration, Osteoclast differentiation and Natural killer cell mediated cytotoxicity. Finally, GO analysis was performed with overlapping genes. Regarding the biological processes (BP), the overlapping genes were significantly enriched in response to lipopolysaccharide, response to molecule of bacterial origin, regulation of angiogenesis, response to oxygen levels, regulation of vasculature development, regulation of response to wounding, response to nutrient, negative regulation of cell migration, negative regulation of cell motility and epithelial cell migration (Fig. 2E). The molecular function (MF) enriched by the overlapping genes included ligand-dependent nuclear receptor transcription coactivator activity, peptidase regulator activity, transcription coactivator activity, long-chain fatty acid binding, RNA polymerase II transcription factor activity, sequence-specific transcription regulatory region DNA binding, transcription factor activity, sequence-specific DNA binding transcription factor recruiting, fatty acid binding, transcription coactivator activity, transcription factor recruiting, peptidase activator activity, nuclear receptor activity (Fig. 2F). In the cellular component (CC), the analysis revealed that enrichment mainly occurred at membrane raft, membrane microdomain, membrane region, caveola, plasma membrane raft (Fig. 2G).

Correlation analysis and prognostic analysis of overlapping genes in GEPIA

We used the GEPIA database to analyze whether 17 overlapping genes are related to the prognosis of patients with AML recurrence (Supplementary Fig. 1). P value < 0.05 was considered statistically significant. We found that the *CXCL 10* gene is associated with the prognosis of patients with relapsed AML (Fig. 3A). We found that *CXCL 10* is the target of quercetin, and we speculate that quercetin can improve the prognosis of patients with relapsed drug-resistant AML. Compared with primary AML patients, *CXCL 10* expression is low in relapsed patients, and low *CXCL 10* expression is an independent predictor of poor prognosis in relapsed patients. Then we used *CXCL 10* to analyze the correlation with 17 overlapping genes, and found that *HMOX1*, *IRF1* and *CXCL 10* have a high correlation ($R > 0.5$) (Fig. 3B, 3C).

Molecular docking

The structure of *CXCL 10* and quercetin were introduced into AutoDockTools for molecular docking. In general, the lower the binding free energy, the more stable the binding between the ligand and protein receptor. According to the results of molecular docking, we found that quercetin has a strong binding activity with *CXCL 10* (Fig. 4).

Discussion

Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is a highly heterogeneous and fatal disease[37]. At present, the main method of treatment of AML is chemotherapy, but patients who relapse often develop resistance and are not sensitive to chemotherapy. Finding new therapeutic drugs and targets is the key to improving drug resistance. In this study, we analyzed the active ingredients and targets of the drug in Jieduhuayu Decoction based on the network pharmacology of Chinese medicine, and analyzed the differential genes between patients with relapsed drug-resistant AML and patients with primary AML through the GEO dataset to find methods to improve AML resistance.

This study is the first bioinformatics study to report the relationship between TCM network pharmacology and AML relapsed drug resistance differential genes. Through the differential gene screening of Chinese medicine network pharmacology and GEO database, we finally found 17 coincident genes, and found that 16 of these 17 coincident genes are the target genes of quercetin. By analyzing 17 overlapping genes, we found that *CXCL 10* is related to the prognosis of AML patients with relapsed resistance. Low expression of *CXCL 10* in patients with relapsed resistance indicates a poor prognosis. And through the correlation analysis of 17 overlapping genes, we found that *HMOX1*, *IRF1* and *CXCL 10* have a good correlation. Therefore, we believe that quercetin affects the prognosis of patients with AML relapsed resistance by targeting *CXCL 10*.

CXC chemokine ligand 10 (*CXCL 10*), also known as interferon- γ -inducible protein 10 (IP-10), is one of the CXC chemokine superfamily, which can regulate immune response, angiogenesis, Apoptosis and other effects are related to the occurrence, development, treatment, and prognosis of various tumors[38, 39]. Studies have shown that *CXCL 10* is related to cancer prognosis. Breast cancer patients with high *CXCL 10* expression have a higher survival rate than breast cancer patients with low *CXCL 10* expression. *CXCL 10* can be used as a beneficial predictor of tamoxifen in the treatment of breast cancer[40]. Research on rectal cancer shows that the high expression of *CXCL 10* has high treatment sensitivity, and *CXCL 10* is related to the efficacy and prognosis of rectal cancer[41]. Studies on tongue cancer have shown that the expression of *CXCL 10* has a significant correlation with the efficacy of radiotherapy for tongue cancer. The higher the expression of *CXCL 10*, the better the efficacy, which can be used as an evaluation index for the prognosis and overall survival rate of radiotherapy for tongue cancer[42]. Combined with previous studies and the results of our bio-analysis, we have reason to believe that targeting *CXCL 10* with quercetin can improve the prognosis of AML patients. Heme oxygenase-1 (*HMOX1*), as a key protein in oxidative stress, is related to the degradation of heme into biliverdin, iron and carbon monoxide[43]. Studies have found that *HMOX1* is one of the most important mechanisms leading to AML chemotherapy resistance, and *HMOX1* can inhibit cell apoptosis by activating the JNK/c-JUN signaling pathway[44]. Studies have found that *HMOX1* can regulate the expression of *CXCL 10* in colon cancer[45]. Interferon regulatory factor (IRF), an important type of transcriptional regulator, has a variety of functions in the regulation of gene expression during inflammation, immune response, cell proliferation, cell cycle progression, T cell differentiation and DNA damage[46]. Studies have shown that the up-regulation of *IRF-1* in cancer foci is considered to be a way to improve the prognosis and reduce the resistance to immunotherapy; and it has been found that IRF-1 response genes can reduce the risk of AML[47]. Some studies have shown that IRF1 plays a role in the corneal innate immune response by regulating the

expression of *CXCL 10*[48]. Combined with our research findings, *HMOX1*, *IRF1* and *CXCL 10* have a high correlation in AML patients. We speculate that *HMOX1* and *IRF1* may participate in *CXCL 10* to improve the prognosis of AML patients with relapsed drug resistance. At the same time, we also found that *HMOX1*, *IRF1* and *CXCL 10* are all target genes of quercetin.

This study had several limitations: (1) the relatively small number of cases evaluated; (2) The pathway of the study has not been validated in vivo and in vitro experiments.

Conclusion

In summary, through a comprehensive analysis of gene expression and Chinese medicine network pharmacology, we have identified multiple abnormally expressed genes and pathways that may be related to AML relapse and drug resistance.

Declarations

Ethical Approval and Consent to participate

Not applicable

Availability of data and materials

Two gene expression datasets (GSE66525) that support the findings of this study are available in Gene Expression Omnibus (GEO) at [<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE66525>].

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Competing interests

The authors declared that they have no competing interests.

Authors' contributions

LINJUN HU, QILIANG LU, YANG LIU, and JUNJUN ZHAO conceived the project and wrote the manuscript. ZHI ZENG, ZHAN SHI, and ZUNQIANG XIAO participated in data analysis. QIURAN XU participated in

discussion and language editing. XIONGMIN TONG reviewed the manuscript.

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Consent for publication

The authors agreed to publish the manuscript.

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Figures

Figure 1

Identification of differentially expressed genes in gene expression datasets (GSE66525). (A) Heat map; (B) Volcano map.

Figure 2

17 overlapping genes. (A) The active ingredients of drugs corresponding to overlapping genes; (B) Quercetin molecular formula; (C) PPI network of 17 overlapping genes; (D) KEGG pathway analysis; (E) GO analysis: the biological processes (BP); (F) GO analysis: the molecular function (MF); (G) GO analysis: the cellular component (CC).

Figure 3

Correlation analysis and prognostic analysis of overlapping genes in GEPIA. (A) Prognosis of CXCL10; (B) Correlation analysis between CXCL10 and HMOX1; (C) Correlation analysis between CXCL10 and IRF1.

Figure 4

Molecular docking of CXCL10 with quercetin.

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