MEDS Chinese Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2022.040803
ISSN 2616-1753 Vol. 4 Num. 8

Differential Genes and Traditional Chinese Medicine Prediction of Dilated Cardiomyopathy Were Analyzed Based on Bioinformatics

Weijia Chen[1,a], Zhizheng Xing[2,b], Liangyu Cui[2,c], Yuying Qi[2,d], Jing Ma[2,e,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Department of Traditional Chinese Medicine, Xijing Hospital, Air Force Medical University, Xi'an Shaanxi, 710032, China
[a]765196907@qq.com, [b]mr_xingzz@163.com, [c]cuiliangyu001@126.com, [d]2256160852@qq.com, [e]jingma@fmmu.edu.cn
**Corresponding author*

Keywords: Dilated Cardiomyopathy, Bioinformatics, Traditional Chinese Medicine Prediction, Differentially Expressed Gene

Abstract: **Objective:** To screen the key genes and signal pathways of Dilated cardiomyopathy (DCM) by bioinformatics method and predict the potential TCM for the treatment of DCM. Methods: The Gene Expression Omnibus (GEO) data platform was used to screen the original Gene chip dataset GSE120895 as a sample for research, and the differences of GSE120895 were analyzed by LimMA package of R software. After data quality correction, the key genes in the differential genes were determined by Degree score. Key genes were imported into DAVID database for gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. STRING database and Cytoscape software were used to construct and analyze the protein-protein interaction network (PPI) of key genes. The key genes were screened by Coremine Medical database to predict the potential therapeutic effect of traditional Chinese medicine for DCM. The chemical components of traditional Chinese medicine were obtained from TCMSP database, and Cytoscape was used to construct the "drug-active ingredient-target" network diagram. **Results:** There were 55 differentially expressed genes in dataset GSE120895, Fifteen key genes (CHGB, DBNL, FGFR2, GABRA4, IGFBP2, LINGO1, MME, NES, NPPA, RGS4, SERPINE2, SERTM1, SH3GL2, SNCA, TAGLN) were screened out. GO analysis results showed that key genes in biological processes (BP) were mainly enriched in the negative regulation of neuronal apoptosis, response to lipopolysaccharide, and central nervous system development. In the cellular component (CC), it was mainly enriched in the perinuclear region of cytoplasm, presynaptic cells and polymer complex. In molecular function (MF), high enrichment is related to receptor binding and hormone activity. KEGG enrichment results showed that key genes were mainly enriched in the phosphatidylinositol 3-kinase (PI3K) /AKT (protein kinase B) signaling pathway. Through the screening of key genes, we found salvia miltiorrhiae, ginseng, silkworm sand, corn balsam and other traditional Chinese medicines with potential curative effects, and the above traditional Chinese medicines are closely related to PTGS2, SCN5A, CHRNA7, CHRM1 and other targets. **Conclusions:** This study screened the differentially expressed genes of DCM, identified the key genes in DCM and the potential therapeutic effect of traditional Chinese medicine, which provides a new direction for the clinical treatment of

DCM target and prescription, and also provides a reliable experimental basis for the prevention and treatment of DCM by traditional Chinese medicine.

Dilated cardiomyopathy (Dilated cardiomyopathy, DCM), It is relatively difficult to treat heterogeneous cardiomyopathy, with the characteristics of prolonged and difficult to heal, recurrent attacks, etc., and its morbidity and mortality rate have remained high [1,2], It is also one of the important causes of progressive heart failure. The main clinical manifestations of DCM are: gradual enlargement of the ventricular wall of the heart, decreased ventricular systolic function, heart failure, ventricular and supraventricular arrhythmias, conduction system abnormalities, thromboembolism, and sudden death.2018 edition “Guidelines for the diagnosis and treatment of dilated cardiomyopathy in China” It is pointed out that the commonly used drugs are: Angiotonin Receptor Blocker (ARB), Enkephalin inhibitors, sacupatril and angiotensin-II receptor antagonists、Calcium channel blockers(CCB), β receptor blockers, Angiotensin converting enzyme inhibitor(ACEI)and other drugs [3]. Focusing on the effective control of arrhythmias and the prevention of heart failure, the incidence of adverse cardiovascular events in patients is reduced, the quality of life of patients is improved, and the survival rate of patients is improved [4]. Looking at the classic ancient books of traditional Chinese medicine in the past, the name of dilated cardiomyopathy is not seen, but according to its related symptoms and signs, it can be included in the categories of "heart failure" and "heart palsy" [5-7], At present, the understanding of the disease by various doctors tends to be consistent. There are also a large number of studies that show that Chinese medicine has unique advantages in alleviating symptoms, improving cardiac function, and improving patients' quality of life in the treatment of dilated cardiomyopathy [8-10], however, there are still some mechanism targets that have not been elucidated during treatment. Bioinformatics is an emerging interdisciplinary discipline with essential applications in both translational medicine and precision medicine, and bioinformatics can better help us solve problems such as unclear interpretation of TCM at the microscopic level [11,12], therefore, this study combines bioinformatics and network pharmacology to screen the key genes of dilated cardiomyopathy, target and prediction of traditional Chinese medicine, in order to provide a scientific basis for the mechanism of traditional Chinese medicine in the treatment of dilated cardiomyopathy, and provide a reference for prescription drugs in clinical treatment.

1. Materials and Methods

1.1. Chip Retrieval

Leverage GEO database (https://www.ncbi.nlm.nih.gov/geo/), according to the "Dilated cardiomyopathy" search, the species is screened for human gene expression chips, and the gene expression chip GSE120895 is studied in the dataset to study the correlation between the clinical parameters of dilated cardiomyopathy and myocardial gene expression, and the expression spectrum chip is used as the final research sample, and the expression matrix and related information of the gene expression spectrum chip are downloaded.

1.2. Chip Data Quality Assessment and Standardization

In order to make up for the influence of some of the systematic biases on the data and make it

possible to compare between different genes, the original data is imported and standardized for processing. Use the "R" software to evaluate and standardize the chip data quality. Data normalization is evaluated with data preprocessing results, which are plotted with the R package ggplot2.

1.3. Differential Gene Expression Analysis

Chip analysis of GEO via limma package and online differential expression analysis using the online analysis software GEO2R. After the analysis is completed, the "gene expression matrix" and "gene difference calculation result" are obtained, and the difference gene is defined according to the gene difference expression amount by 2 times, and the corrected p-value is less than 0.05, and the difference gene list (FC in log2FC is the fold change, which represents the ratio of expression between two samples (groups), and the logarithm with 2 as the base is log2FC. Generally, the absolute value of log2FC is greater than 1 by default for the screening criteria of the difference gene; FDR, or False Discovery Rate, is obtained by correcting the difference significance p-value. Since the differential expression analysis of transcriptome sequencing is an independent statistical hypothesis test for a large number of gene expression values, there will be false positive problems, so in the process of differential expression analysis, the recognized Benjamini-Hochberg correction method is used to correct of differential expression gene screening. FDR<0.01 or 0.05 is generally taken as the default standard. The selection of these two indicators is generally filtered according to empirical values, and it is not completely impossible to adjust. In experiments, the number of genes is too low or too high, and the indicators can be fine-tuned).

1.4. Key Gene Screening and Correlation Analysis

Introduce the difference gene into Cytoscap 3.8.2, using the CytoHubba plug-in, to rank nodes by Degree, with the top 15 named Hub genes. In addition, the expression level and co-expression of key genes in dilated cardiomyopathy were observed, and the expression of key genes in dilated cardiomyopathy was analyzed.

1.5. Genome Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment Analysis

In order to further determine the potential function of key genes, the key genes were imported into the DAVID database (http://david.ncifcrf.gov/) for GO and KEGG enrichment analysis, and the species was selected as human (Homo spaiens), and the biological processes, cellular components and molecular functions of dilated cardiomyopathy were analyzed to explore its pathological mechanism.

1.6. Protein Protein Interwork (PPI) Network Construction

The obtained key genes are imported into the STRING database (http://cn.string-db.org) for PPI analysis, the species is set to "homo sapiens", and PPI network construction is carried out after the introduction of Cytoscape software.

1.7. Chinese medicine prediction

Enter the key genes into the Coremine Medical database (https://www.coremine. com/medical/), download the relevant Chinese medicine information of the gene, and determine the Chinese

medicine with potential treatment DCM under the condition of P<0.05. At the same time, according to the conditions of biological oral availability (OB) ≥30% and drug-like (DL) ≥0.18 in the TCMSP database, the active chemical components of traditional Chinese medicine are predicted, the target of action of the corresponding components is extracted, and the data is imported into Cytoscape to build a network diagram of "Chinese medicine-active ingredient-target" by using the Uniprot database to deduplicate and normalize the obtained effective targets, and the degree algorithm in the CytoHubba plug-in is used to rank the top 15 The target is screened and visualized.

2. Outcome

2.1. Chip Data Quality Assessment and Standardization

The original data of GSE120895 chip was evaluated and standardized to obtain a boxplot, and the results showed that the relative logarithmic expression values of 8 chip samples and 47 dilated cardiomyopathy chip samples in the corrected control group were placed in the vertical center, and the median was the same, indicating that the chip quality was good and comparable. (Figure 1-2)

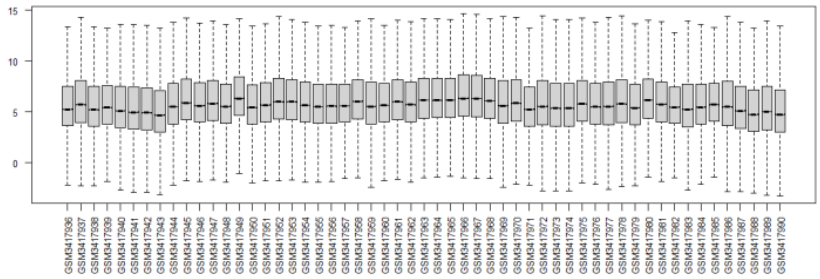

Figure 1: Before chip data correction

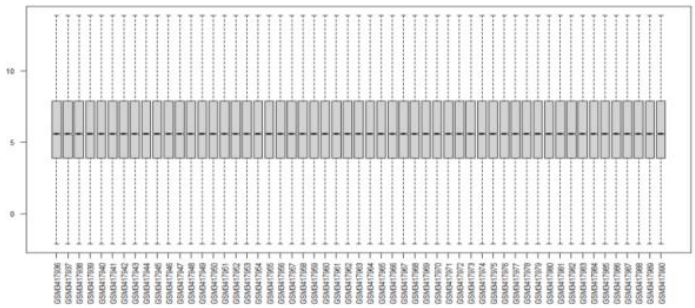

Figure 2: After the chip data is corrected

2.2. Differential Expression Gene Screening Results

The samples of the DCM group were compared with the control group, and the filter conditions were log2FC=1, P<0.05, and the rstudio software was applied for analysis, and the calculation results of all genes were visualized to obtain volcano maps, and the difference genes were visualized to obtain heat maps. 55 differential genes were obtained in GSE120895, including 29 upregulated genes and 26 downregulated genes. The following two pictures can understand the overall distribution of differentially expressed genes, the more the horizontal axis of Figure 3 is distributed on both sides, the greater the difference multiple, the more upward the vertical axis, the smaller the q value, and the stronger the significance. The green dot on the left is the difference gene that is significantly downregulated, and the red dot on the right is the difference gene that is

significantly upregulated. In Figure 4, the greener the color, the higher the gene expression, and the lower the color crimson.

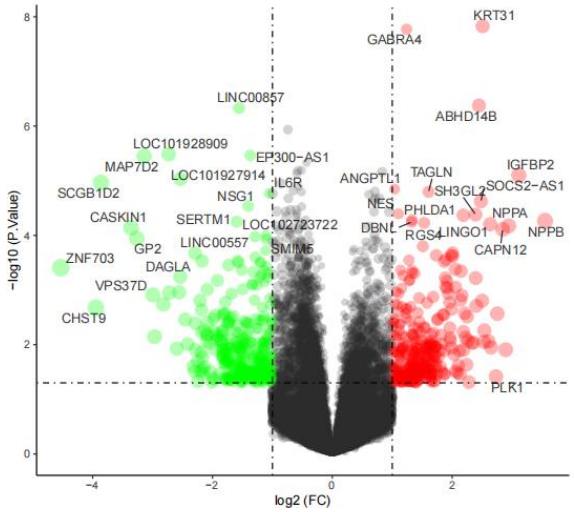

Figure 3: Differential expression gene volcano map

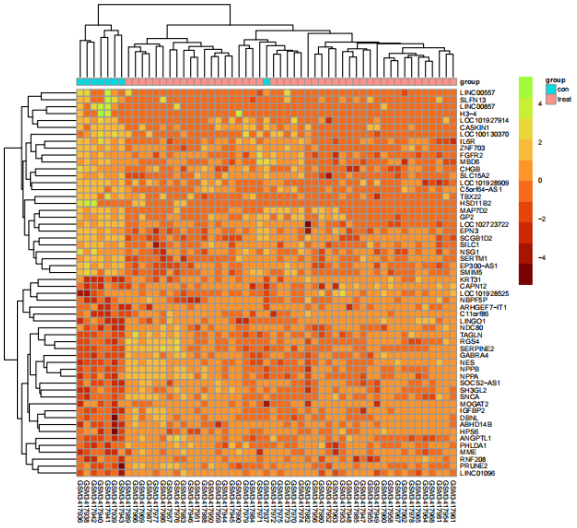

Figure 4: Differential expression gene heat map

2.3. Key Gene Screening and Correlation Analysis

The first 15 key genes (Hub gene) are: 15 key genes (CHGB, DBNL, FGFR2, GABRA4, IGFBP2, LINGO1, MME, NES, NPPA, RGS4, SERPINE2, SERTM1, SH3GL2, SNCA, TAGLN). 15 key genes were correlated with analysis. The horizontal coordinate in the figure is the name of the key gene, where the deeper the blue circle, the stronger the positive correlation between the 2 genes in dilated cardiomyopathy, and the deeper the red circle, the stronger the negative correlation and the stronger the correlation can be seen from Figure 5, the correlation of the 15 key genes is weak, the correlation coefficient > 0.5, in order from high to low: RGS4(0.84), NPPA(0.71), NES(0.67), SNCA(0.63), GABRA4(0.57), DBNL(0.54), CHGB(0.53), LINGO1(0.50).

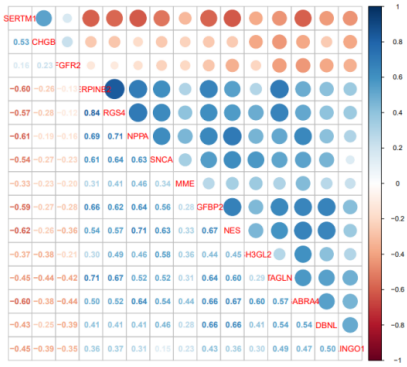

Figure 5: Correlation analysis of key genes

2.4. Genome Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

The key genes obtained above were used in the DAVID Database (https://david.ncifcrf.gov) database for go function and enrichment of KEGG pathways. The results of GO analysis show (Figure 6): In the biological process (BP), the main enrichment is in the negative regulation of neuronal apoptosis, response to lipopolysaccharides, and central nervous system development. In the cellular component (CC), mainly enriched in the perinuclear region of the cytoplasm, presynaptic cells, polymer complexes; in molecular function (MF), high enrichment is associated with receptor binding and hormonal activity. In the KEGG enrichment results (Figure 7), key genes are mainly enriched in the phosphatidylinositol 3 kinase (PI3K)/AKT (protein kinase B) signaling pathway, PI3K/AKT signaling pathway map (Figure 8).

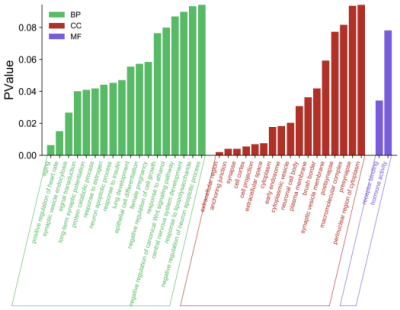

Figure 6: GO Enrichment analysis

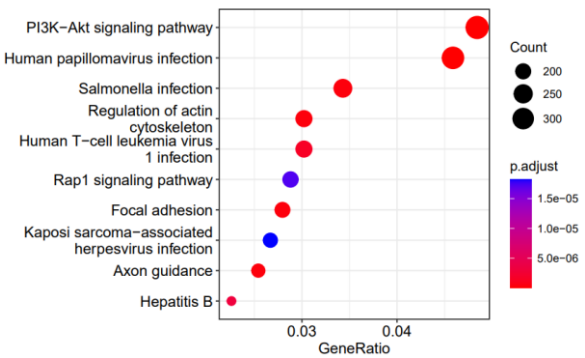

Figure 7: KEGG Enrichment analysis

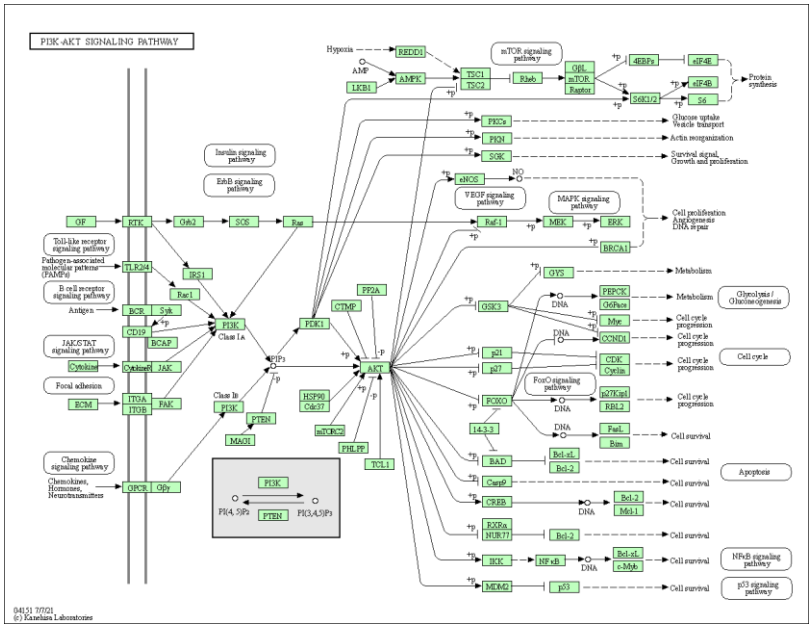

Figure 8: PI3K-AKT Signal pathway diagram

2.5. Construction and Analysis of PPI Networks

The 15 key differentially expressed genes were imported into the STRING database, Cytoscape 3.9.0 online plotted interacting network diagram, and the MCC algorithm of the plug-in cytoHubba was used to visualize the Top15 hub genes (see Figure 9), where the shade of color represented the level of MCC score, and the darker color, the more important it was.

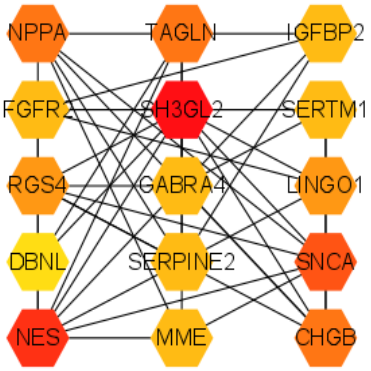

Figure 9: Interacting network diagram

2.6. Predicted Results of Potential Chinese Medicines

After screening at Coremine Medical and found that the four Chinese medicines with the highest frequency of acting on key genes of DCM were danshen, ginseng, silkworm sand, and corn whiskers (hereinafter referred to as DS, RS, CS, YMX). This Sanwei Chinese medicine is the role of multiple key genes, and its related active ingredients may be potential Chinese medicines for the treatment of diseases. Therefore, the above 3 flavors of traditional Chinese medicine are selected, and the active ingredients of Chinese medicine are screened through the TCMSP website with OB≥30%, DL≥0.18 as the condition. 22 active ingredients of ginseng, 64 active ingredients of

danshen, 4 active ingredients of silkworm sand, and 12 active ingredients of corn whiskers were obtained. The resulting data are collated and imported into the Cytoscape 3.9.0 software to draw a network diagram of "Chinese Medicine-Active Ingredient-Target of Action" (see Figures 10 and 11).

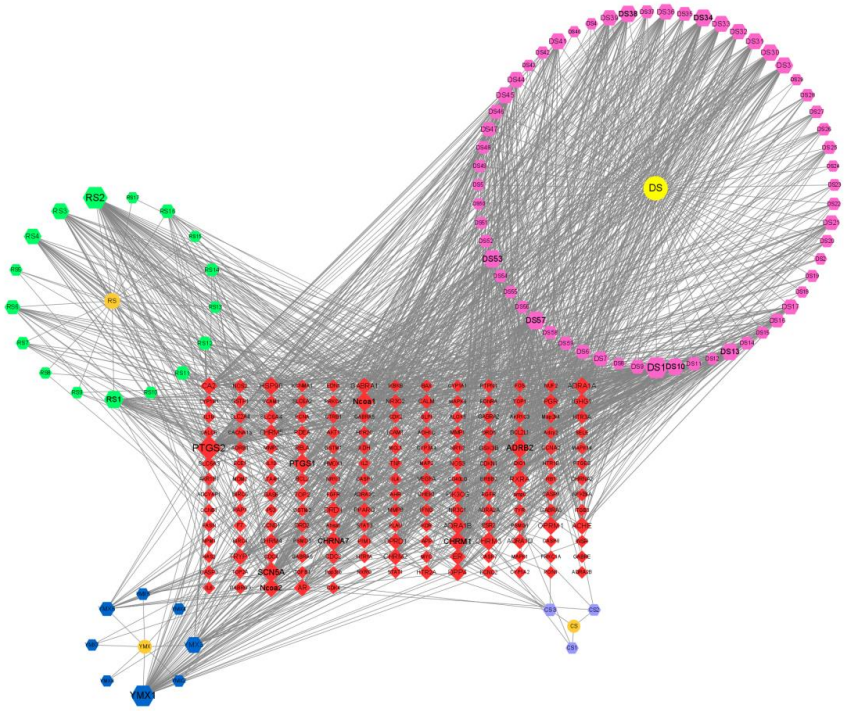

Figure 10: Traditional Chinese Medicine-Active Ingredient-Target Network Diagram

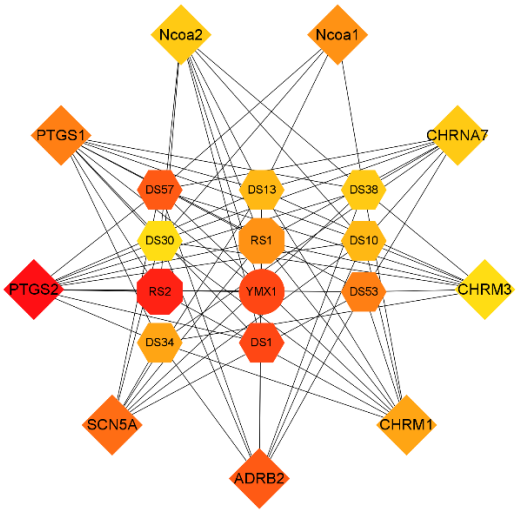

Figure 11: Network map of key targets of active ingredients of traditional Chinese medicine in the treatment of dilated cardiomyopathy

3. Conclusions

3.1. Differential Expression of Genes between DCM Patients and Healthy People

The pathogenesis of dilated cardiomyopathy (DCM) is complex, with most of its main pathogenesis being infection, inflammation, and metabolic and endocrine disorders caused by myocarditis, alcohol, drugs, and toxins [13]. Studies have also shown that DCM patients account for 30-40% of all heart failure cases, which is also an important cause of sudden cardiac death and heart failure [14]. So far, about 40 pathogenic variants have been found in genes that cause DCM [15], this also suggests that using genetic analysis to determine the causative factors of DCM remains a challenge.

This study extracted the information of chip GSE120895, analyzed by bioinformatics method, screened out 55 differentially expressed genes in patients with dilated cardiomyopathy and healthy people, and screened out the top 15 key genes by PPI, namely: CHGB, DBNL, FGFR2, GABRA4, IGFBP2, LINGO1, MME, NES, NPPA, RGS4, SERPINE2, SERTM1, SH3GL2, SNCA, TAGLN, and suggests that these genes may play an important role in the DCM mechanism. Chromogranin B (CHGB) is an emerging cardiovascular biomarker that regulates the production of b-type natriuretic peptide (BNP), and more studies have shown that CHGB levels are significantly higher in patients with heart failure[16]. Insulin-like growth factor-binding protein 2 (IGFBP2), the primary insulin-like growth factor-binding protein produced by white adipose tissue, has been significantly associated with all-cause mortality [17]. Our study showed that the expression level of IGFBP2 in the DCM sample was regulated upwards compared to healthy human samples. ANP (atrial natriuretic peptide) and BNP (type B natriuretic peptide) encoded by NPPA are important indicators of prognosis, diagnosis, and treatment of heart disease. At the same time, NPPA is also a gene necessary to prevent premature heart hypertrophy [18]. SERPINE2 is encoded by the SERPINE2 gene on human chromosome 2q99-q354, also known as protease neuroprotein 1 (PN-1). SERPINE2 is expressed in fibroblasts, vascular smooth muscle cells, endothelial cells, and other cells. While the mechanism of action of SERPINE2 in cardiac fibrosis may not have been fully established, SERPINE2 increases collagen deposition and is also a key factor in causing cardiac fibrosis [19].

3.2. Myocardial Fibrosis and Apoptosis are Important Parts of DCM Progression

Through the analysis of key expression genes, the main pathways involving SERPINE2 and FGFR2 are related to cell fibrosis, and IGFBP2 is one of the classic signaling pathways for apoptosis, which further shows that DCM is closely related to myocardial fibrosis and apoptosis.Of these, FGFR2 (Fibroblast Growth Factor-2) is a growth factor expressed by both myocytes and non-myocytes. Mouse models of FGF-2 deletion indicate [20], FGF-2 secreted by non-cardiomyocytes mediates hypertension or elevated angiotensin II levels, leading to myocardial hypertrophy [21], Studies have determined that human secretion of Hi-FGF-2 affects fibrosis, myofibroblast phenotype, and cardiomyocyte mastification. The downward adjustment of miR-873 upwards the expression of IGFBP2 and promotes the activation of the PI3K/AKT/mTOR axis [22].The heart function of rats was improved, apoptosis of myocardial cells was inhibited, and the activity of superoxide dismutase, carbon monoxide synthase and nitric oxide content was increased.

3.3. DCM Potential Treatment of Herbal Medicine

At present, the early stage of dilated cardiomyopathy is mainly treated with drug therapy, antiarrhythmia, and sudden death, and immunology. Although symptoms can improve to some extent after treatment, hospitalization rates and mortality remain unaddressed [23]. Therefore, in

this study, the key genes were screened for traditional Chinese medicine, and multi-flavored Chinese medicines such as ginseng, danshen, corn, whiskers, and silkworm sand were obtained. In order to further explore the mechanism of the above 4 flavors of traditional Chinese medicine in the treatment of DCM, the network pharmacology analysis was carried out, and it was found that these Chinese medicines were closely related to targets such as PTGS2, SCN5A, CHRNA7, CHRM1, etc., which also corresponded to the Top15 genes screened by our bioinformatics. Danshen and ginseng are commonly used in clinical medicine to tonify qi and activate blood, which is also similar to most modern doctors such as Li Qiaozhi and Li Bin and other researchers [24-26] It is considered that the main symptom of DCM is consistent with "qi deficiency blood stasis certificate". Danshenone II.A has also been found to inhibit galectin-3 protein expression and myocardial fibrosis in rats with ischemic heart failure [27], The level of p-PI3K and p-Akt protein in myocardial tissue in rats with heart failure in tanshinone II.A treatment group decreased. Promotes fibrocyte viability and inhibits activation of the PI3K/Akt signaling pathway to alleviate cardiomyocyte fibrosis, thereby preventing ventricular remodeling from occurring [28]. Ginsenoside Rbl inhibits mRNA expression of doxorubicin-induced cardiac fibrosis-related factors.

In this study, GSE120895 expression spectroscopy chip was processed and analyzed by bioinformatics method, the top 15 key genes of DCM were screened, and the active ingredients of traditional Chinese medicine and its active ingredients were predicted. It is further found that PTGS2, SCN5A, CHRNA7, CHRM1 genes play a role in the development of DCM, so that Chinese medicines such as danshen, ginseng, silkworm sand, corn whiskers and their active ingredients may become new drugs for the treatment of DCM, providing theoretical targets for TCM treatment of DCM, and promoting the development of TCM diagnosis and treatment of DCM, the next step will continue to provide molecular analysis basis and provide a predictive theoretical basis for subsequent experiments.

References

[1] Tabish A M, Azzimato V, Alexiadis A, et al. Genetic epidemiology of titin-truncating variants in the etiology of dilated cardiomyopathy[J]. Biophys Rev, 2017,9(3): 207-223.

[2] Moeinafshar A, Yazdanpanah N, Rezaei N. Diagnostic biomarkers of dilated cardiomyopathy[J]. Immunobiology, 2021,226(6): 152153.

[3] Chinese Society of Cardiovascular Diseases, Chinese Cooperative Group of Myocarditis Cardiomyopathy. Guidelines for diagnosis and treatment of dilated cardiomyopathy in China[J]. Journal of Clinical Cardiovascular Diseases, 2018,34(05): 421-434.

[4] Wang Chuangshi, Wang Yang, Yang Jingang, et al. Recommended classification and evidence level analysis of major cardiovascular guidelines in China in the past decade[J]. Chinese Circular Magazine, 2020,35(09): 880-887.

[5] Zhu Zhenzhen, Yuan Canyu, Yuan Zhiyu, et al. Exploration of paleopathyms of heart failure[J]. Chinese Journal of Basic Medicine of Traditional Chinese Medicine, 2017,23(11): 1509-1511.

[6] Lu Jianqi, Li Suyi, Lu Junshen, et al. Research progress of traditional Chinese medicine in the treatment of chronic heart failure[J]. Chinese Journal of Traditional Chinese Medicine, 2020,38(12): 145-148.

[7] Tan Yuqing, Li Jun, CHEN Hengwen, et al. Re-evaluation of the effect of traditional Chinese medicine in the treatment of dilated cardiomyopathy[J]. Journal of Practical Cardiopulmonary and Vascular Diseases, 2022,30(03): 83-88.

[8] Sheng Lei, Hu Liangyan, Hong Lifeng. Efficacy of Linggui Yangxin Decoction in the Treatment of Dilated Cardiomyopathy with Heart Qi and Yang Deficiency and Its Effect on Anti-myocardial Antibodies[J]. Journal of Modern Integrative Medicine, 2018, 27(25): 2807-2810.

[9] Bai Chunyu, Xu Hongzun. Efficacy of irbesartan combined with astragalus baoxin decoction in the treatment of dilated cardiomyopathy[J]. Journal of Traditional Chinese Medicine, 2018,33(04): 648-652.

[10] Chen Ming. Integrated Bioinformatics in the Era of Big Data[J]. bioinformatics, 2022,20(02): 75-83.

[11] Liu Huaiquan, Zhou Fangfang, Zhang Yupei, et al. Application prospect of bioinformatics in basic research of integrated traditional Chinese and Western medicine[J]. Journal of Hubei University for Nationalities (Medical Sciences), 2020,37(02): 49-52.

[12] Chen S N, Mestroni L, Taylor M. Genetics of dilated cardiomyopathy[J]. Curr Opin Cardiol, 2021,36(3): 288-294.

[13] LIU L, SUN K, ZHANG X, et al. Advances in the role and mechanism of BAG3 in dilated cardiomyopathy[J]. Heart Fail Rev, 2021,26(1): 183-194.
[14] NGUYEN T V, TRAN V M, DO T, et al. Genetic Determinants and Genotype-Phenotype Correlations in Vietnamese Patients With Dilated Cardiomyopathy[J]. Circ J, 2021,85(9): 1469-1478.
[15] HEIDRICH F M, MELZ C, BUECHAU M S, et al. Regulation of circulating chromogranin B levels in heart failure[J]. Biomarkers, 2018,23(1): 78-87.
[16] HO J E, LYASS A, COURCHESNE P, et al. Protein Biomarkers of Cardiovascular Disease and Mortality in the Community[J]. J Am Heart Assoc, 2018,7(14).
[17] MAN J, van DUIJVENBODEN K, KRIJGER P, et al. Genetic Dissection of a Super Enhancer Controlling the Nppa-Nppb Cluster in the Heart[J]. Circ Res, 2021,128(1): 115-129.
[18] LI X, ZHAO D, GUO Z, et al. Overexpression of SerpinE2/protease nexin-1 Contribute to Pathological Cardiac Fibrosis via increasing Collagen Deposition[J]. Sci Rep, 2016, 6: 37635.
[19] SANTIAGO J J, MCNAUGHTON L J, KOLEINI N, et al. High molecular weight fibroblast growth factor-2 in the human heart is a potential target for prevention of cardiac remodeling[J]. PLoS One, 2014, 9(5): e97281.
[20] SVYSTONYUK D A, NGU J M, MEWHORT H E, et al. Fibroblast growth factor-2 regulates human cardiac myofibroblast-mediated extracellular matrix remodeling[J]. J Transl Med, 2015, 13: 147.
[21] HAN N, FANG H Y, JIANG J X, et al. Downregulation of microRNA-873 attenuates insulin resistance and myocardial injury in rats with gestational diabetes mellitus by upregulating IGFBP2[J]. Am J Physiol Endocrinol Metab, 2020, 318(5): E723-E735.
[22] HU Shengshou, GAO Runlin, LIU Lisheng, et al. Overview of China Cardiovascular Disease Report 2018[J]. Chinese Journal of Circulation, 2019, 34(03): 209-220.
[23] LI Qiaozhi, WANG Zhentao, GUO Zongyao. Progress in the treatment of qi deficiency and blood stasis in dilated cardiomyopathy from the theory of "energy hunger"[J]. World Science and Technology - Modernization of Traditional Chinese Medicine, 2022: 1-6.
[24] LI Bin. Effect of anti-fibribratory formula on myocardial function and neuroendocrine factors in patients with dilated cardiomyopathy (qi deficiency and blood stasis) complicated with heart failure [J]. New TCM, 2020, 52(16): 51-55.
[25] ZHANG Huichao, WANG Zhentao, HAN Lihua, et al. Literature on TCM symptoms and medication rules of dilated cardiomyopathy [J]. New Chinese medicine, 2021, 53(23): 13-17.
[26] FENG Jun, CHEN Huawen. Effects of tanshinone II.A on myocardial remodeling in chronic heart failure by regulating miR-133 levels [J]. Journal of Modern Integrated Traditional Chinese and Western Medicine, 2016, 25(08): 803-806.
[27] SONG Yuanyuan, SHI Pengxiao, YAN Hongjuan. Effects of tanshinone II.A on ventricular remodeling and PI3K/Akt signaling pathway in rats with heart failure [J]. Journal of Integrative Cardiovascular and Cerebrovascular Diseases, 2022, 20(04): 638-642.
[28] KONG Hongliang, SONG Lijie, LI Zhanquan, et al. Effect of ginsenoside Rbl on the expression of cardiac fibrosis-causing factors in rats with doxorubicin heart failure [J]. Journal of Nanjing Medical University (Natural Science Edition), 2012, 32(01): 26-29.