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High expression of CASP1 induces atherosclerosis

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Abstract

Atherosclerosis is a chronic, progressive vascular disease. The relationship between CASP1 gene expression and atherosclerosis remains unclear. The atherosclerosis dataset GSE132651 and GSE202625 profiles were downloaded from gene expression omnibus. Differentially expressed genes (DEGs) were screened. The construction and analysis of protein–protein interaction network, functional enrichment analysis, gene set enrichment analysis, and Comparative Toxicogenomics Database analysis were performed. Gene expression heatmap was drawn. TargetScan was used to screen miRNAs that regulate central DEG. 47 DEGs were identified. According to gene ontology analysis, they were mainly enriched in the regulation of stimulus response, response to organic matter, extracellular region, extracellular region, and the same protein binding. Kyoto Encyclopedia of Gene and Genome analysis results showed that the target cells were mainly enriched in the PI3K-Akt signaling pathway, Ras signaling pathway, and PPAR signaling pathway. In the enrichment project of Metascape, vascular development, regulation of body fluid levels, and positive regulation of cell motility can be seen in the gene ontology enrichment project. Eleven core genes (CASP1, NLRP3, MRC1, IRS1, PPARG, APOE, IL13, FGF2, CCR2, ICAM1, HIF1A) were obtained. IRS1, PPARG, APOE, FGF2, CCR2, and HIF1A genes are identified as core genes. Gene expression heatmap showed that CASP1 was highly expressed in atherosclerosis samples and low expressed in normal samples. NLRP3, MRC1, IRS1, PPARG, APOE, IL13, FGF2, CCR2, ICAM1, HIF1A were low expressed in atherosclerosis samples. CTD analysis showed that 5 genes (CASP1, NLRP3, CCR2, ICAM1, HIF1A) were found to be associated with pneumonia, inflammation, cardiac enlargement, and tumor invasiveness. CASP1 gene is highly expressed in atherosclerosis. The higher the CASP1 gene, the worse the prognosis.

Abbreviations: Caspase-1 = cysteine protease 1, CTD = Comparative Toxicogenomics Database, DEGs = differentially expressed genes, FC = fold change, FDR = false discovery rate, GEO = gene expression omnibus, GO = gene ontology, GSEA = gene set enrichment analysis, KEGG = Kyoto Encyclopedia of Gene and Genome, LDL-C = low density lipoprotein cholesterol, PPI = protein–protein interaction, STRING = Search Tool for the Retrieval of Interacting Genes.

Keywords: atherosclerosis, bioinformatics, CASP1, differentially expressed genes

1. Introduction

Atherosclerosis is a chronic disease. Atherosclerosis is usually more common in middle-aged and elderly people over 50 years of age, with a higher incidence rate in men and a higher prevalence rate in developed countries.[1–3] Atherosclerosis is characterized by the formation of plaques within the arteries. In the development of atherosclerosis, plaque may become unstable. As the plaques continue to grow, the lumen of the artery narrows, causing obstruction of blood flow. Common clinical manifestations of atherosclerosis include heart disease symptoms, stroke symptoms, peripheral artery disease symptoms, kidney disease symptoms, and other symptoms.[4–6] Plaques are mainly composed of cholesterol, lipoprotein, and other blood components, gradually depositing in the inner layer of the arterial wall. Unstable plaques are more likely to rupture and form blood clots, leading to acute vascular occlusion. As the plaques develop, calcium salts can deposit in the plaques, forming calcified plaques.[7–9] Atherosclerosis is a chronic and progressive disease. If it is not intervened and treated in time, it will do great harm. The pathogenesis of atherosclerosis is not clear,

YL and LD contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The data in this article are from public databases and are exempt from ethical review.

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and the disease may be related to genetic factors, chromosome abnormalities, gene fusion, and other factors. Therefore, it is particularly important to study the molecular mechanism of atherosclerosis.

Bioinformatics technology plays an important role in the research of atherosclerosis. Through whole genome sequencing and Transcriptome sequencing, researchers can identify key information, such as pathogenic genes, mutations, and gene expression abnormalities in atherosclerosis. Bioinformatics technology can help to analyze protein interaction networks, functional pathways, and potential protein markers, and help to understand the pathogenesis of atherosclerosis and the discovery of diagnostic markers. Bioinformatics technology provides tools and methods for data management, data mining, and system integration, and can help integrate data from different levels of Genomics, Transcriptome, Proteomics, metabolomics, and so on, so as to discover the molecular characteristics and early markers of atherosclerosis. The development of these bioinformatics technologies provides an important tool and platform for the research of atherosclerosis, helps to reveal its pathogenesis, the discovery of diagnostic markers, and the identification of therapeutic targets, and further promotes the progress of disease diagnosis and treatment.[10]

However, the relationship between CASP1 gene and atherosclerosis is still unclear. Therefore, this paper intends to use bioinformatics technology to mine core genes between atherosclerosis and normal tissues, and conduct enrichment analysis and pathway analysis. The public dataset was used to verify the significant role of CASP1 gene in atherosclerosis. The main purpose of this study is to gain a deeper understanding of the molecular mechanism of atherosclerosis, discover potential diagnostic markers, and find new therapeutic targets. CASP1 plays an important role in immune regulation and may be related to atherosclerosis. This study is important to the field of atherosclerosis and is expected to fill current knowledge gaps and provide new insights into the treatment and diagnosis of atherosclerosis.

2. Methods

2.1. Atherosclerosis dataset

In this study, the atherosclerosis dataset GSE132651 and GSE202625 profiles are gene expression omnibus databases generated from GPL96 and GPL23934 and downloaded from http://www.ncbi.nlm.nih.gov/geo/. GSE132651 includes 13 Atherosclerosis and 6 normal samples, and GSE202625 includes 27 atherosclerosis and 25 normal samples to identify differentially expressed genes of atherosclerosis.

2.2. Debatch processing

For the merging and debatching of multiple datasets, we first use the R software package to merge the datasets GSE132651 and GSE202625. For the merging of multiple datasets, we first use the R software package inSilicoMerging [DOI: 10.1186/1471-2105-13-335] to merge the datasets and obtain the merge matrix. Furthermore, we use the removeBatchEffect function of the R software package limma (version 3.42.2,) to remove batch effects and ultimately obtain the matrix after removing batch effects, which is applied to subsequent analysis.

2.3. Screening of differentially expressed genes

The R package "limma" is used for probe aggregation and background correction of the merging matrix of GSE132651 and GSE202625. The Benjamin Hochberg method is used to adjust the original *P* value. Calculate fold change using false discovery rate (FDR). The cutoff value of DEG is $P <$ .05 and FC > 1.5. And make a visual representation of the volcano map.

2.4. Construction and analysis of protein–protein interaction (PPI) network

Search Tool for the Retrieval of Interacting Genes (STRING) database. The aim of db.org/ is to collect, score, and integrate all publicly available sources of PPI information, and supplement these sources by calculating predictions. This study inputted a list of DEGs into the STRING database and constructed a PPI network for predicting core genes (confidence level >0.4). Cytoscape software can provide biologists with biological network analysis and 2-dimensional visualization. This study visualized and predicted core genes in the PPI network formed by the STRING database using Cytoscape software. First, we import the PPI network into the Cytoscape software and use MCODE to find the modules with the best correlation. We also use 2 algorithms (MCC and MNC) to calculate the 10 genes with the best correlation and take the intersection. After visualization, we export the list of core genes.

2.5. Functional enrichment analysis

Gene ontology analysis (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis are computational methods for evaluating gene functions and biological pathways. This study will input the list of differentially identified genes into the KEGG API (https://www.kegg.jp/kegg/rest/keggapi.html). We obtained the latest KEGG Pathway gene annotation as a background and mapped the genes to the background set. We used the R software package clusterProfiler (version 3.14.3) for enrichment analysis to obtain the results of gene set enrichment. We also used the GO annotation of genes in the R software package org.Hs.eg.db (version 3.1.0) as a background to map the genes to the background set, with a minimum gene set of 5 and a maximum gene set of 5000. *P* value of <.05 and a FDR of <0.25 are considered statistically significant measures.

In addition, the Metascape database can provide comprehensive gene list annotations and analysis resources, and visually export them. We used Metascape (http://metascape.org/gp/index.html) Database for functional enrichment analysis and export of the list of DEGs mentioned above.

2.6. Gene set enrich analysis (GSEA)

For GSEA, we derived from GSEA (DOI: 10.1073/pnas.0506580102, http://software.broadinstitute.org/gsea/index.jsp). The website obtained GSEA software (version 3.0), and divided the samples into 2 groups according to atherosclerosis and normal samples, http://www.gsea-msigdb.org/gsea/downloads.jsp. The c2.cp.kegg.v7.4.symbols.gmt subset was downloaded to evaluate the related pathways and molecular mechanisms. Based on the gene expression profiling and phenotype grouping, the minimum gene set was 5, the maximum gene set was 5000, and a thousand resamples, *P* value of <.05 and a FDR of <0.25 were considered statistically significant. And GO and KEGG analyses were conducted on the entire genome. Developed by GSEA.

2.7. Gene expression heatmap

We used R packet heatmap to make a heat map of the expression of core genes in GSE132651 and GSE202625 found by the 2 algorithms in the PPI network, to visualize the difference in the expression of core genes between atherosclerosis and normal samples.

2.8. Comparative Toxicogenomics Database (CTD) analysis

The CTD integrates a large amount of data on chemical substances, genes, functional phenotypes, and interactions between diseases, providing great convenience for the study of disease-related environmental exposure factors and potential drug action mechanisms. We inputted the core genes into the CTD website, identified the most relevant diseases to the core genes, and drew a radar map of the expression differences of each gene using Excel.

2.9. miRNA

TargetScan is an online database used for predicting and analyzing miRNAs and target genes. In our study, TargetScan was used to screen miRNAs that regulate central DEG.

3. Result

3.1. Differentially expressed genes (DEGs) analysis

In this study, 47 DEGs were identified based on the debatch synthesis matrix of GSE132651 and GSE202625 according to the set cutoff values (Fig. 1). We sorted the identified DEGs from small to large *P* values and selected the top 500 for subsequent analysis.

3.2. Functional enrichment analysis

3.2.1. Differentially expressed genes. We conducted GO and KEGG analysis on these DEGs, and according to GO analysis, they were mainly enriched in the regulation of stimulus response, response to organic matter, extracellular region, extracellular region, and the same protein binding (Fig. 2A, C, E).

The KEGG analysis results showed that the target cells were mainly enriched in the PI3K-Akt signaling pathway, Ras signaling pathway, and PPAR signaling pathway (Fig. 2G).

3.2.2. Gene set enrich analysis. In addition, we conducted GSEA enrichment analysis on the entire genome, aiming to identify potential enrichment items in non DEGs and verify the results of DEGs. The intersection of enrichment term and GO KEGG enrichment term of DEGs is shown in the figure, which is mainly enriched in PPAR signaling pathway, ribosome, and cancer pathways (Fig. 2B, D, F, H).

3.2.3. Metascape enrichment analysis. In the enrichment project of Metascape, vascular development, regulation of body fluid levels, and positive regulation of cell motility can be seen in the GO enrichment project (Fig. 3A). At the same time, we also output enrichment networks colored with enrichment terms and *P* values (Figs. 3B, C, and 4), visualizing the correlation and confidence of each enrichment project.

3.3. Construction and analysis of protein–protein interaction (PPI) network

The PPI network of DEGs was constructed from the Search Tool for the STRING online database and analyzed by Cytoscape software (Fig. 5A) to obtain core gene clusters (Fig. 5B). Two different algorithms were used to identify central genes (Fig. 5C, D). The intersection was obtained using Wayne plots, and the union was obtained using Excel (Fig. 6). Eleven core genes (CASP1, NLRP3, MRC1, IRS1, PPARG, APOE, IL13, FGF2, CCR2, ICAM1, HIF1A) were obtained.

At the same time, we also used the Metascape website to output protein interaction networks and identified core modules to verify the PPI network results in the STRING. Among them, IRS1, PPARG, APOE, FGF2, CCR2, and HIF1A genes are identified as core genes.

3.4. Gene expression heatmap

We visualized the calorimetry of core gene expression in samples (Fig. 7). We found that core gene (CASP1) was highly expressed in atherosclerosis samples and low expressed in normal samples. Core genes (NLRP3, MRC1, IRS1, PPARG, APOE, IL13, FGF2, CCR2, ICAM1, HIF1A) were low expressed in atherosclerosis samples, which may have a regulatory effect on atherosclerosis.

3.5. CTD analysis

In this study, we inputted the list of core genes into the CTD website to search for diseases related to core genes, improving our understanding of the association between genes and diseases. Five genes (CASP1, NLRP3, CCR2, ICAM1, HIF1A) were found to be associated with pneumonia, inflammation, cardiac enlargement, and tumor invasiveness (Fig. 8).

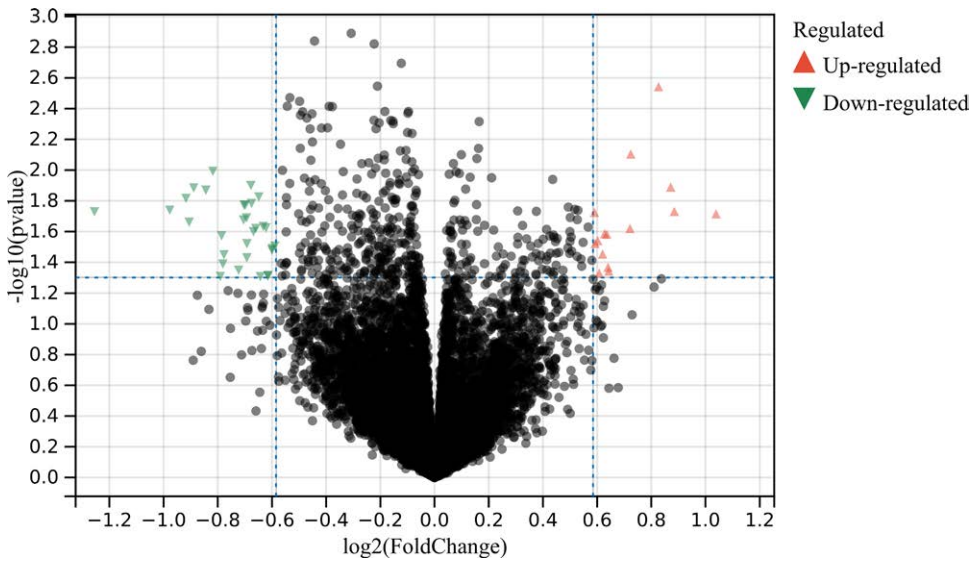

Figure 1. Differentially expressed genes analysis. **About** 47 DEGs were identified.

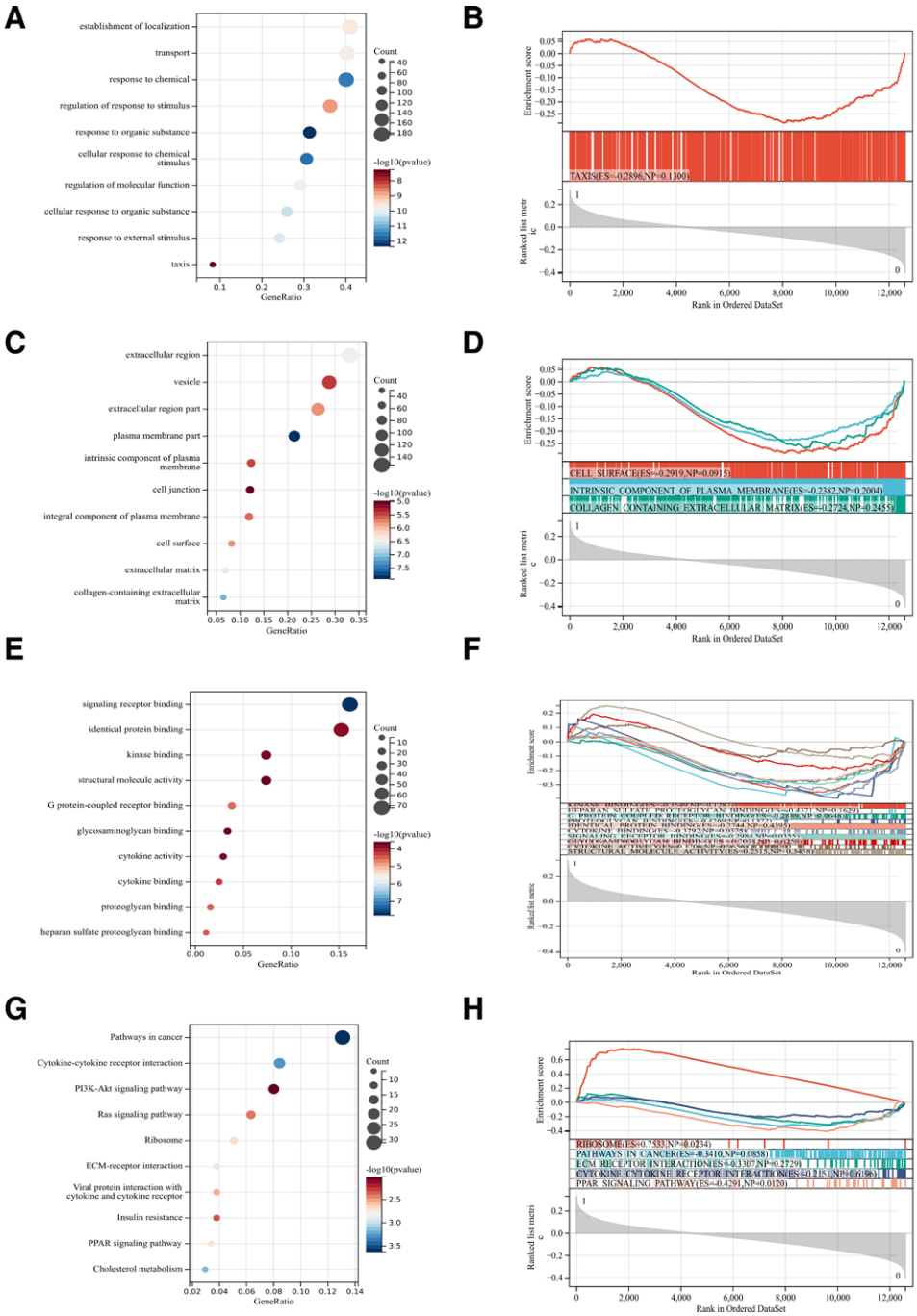

Figure 2. Functional enrichment analysis. (A, C, E) GO. (G) KEGG. (B, D, F, H) GSEA.

3.6. Prediction and functional annotation of miRNAs related to hub genes

In this study, we input a list of hub genes into TargetScan to search for relevant miRNAs and improve our understanding of gene expression regulation (Table 1). We found that the miRNA associated with the NLRP3 gene is hsa-miR-223-3p; The related miRNAs of MRC1 gene are hsa-miR-23c, hsa-miR-130a-5p, and hsa-miR-23a-3p; The miRNA associated with the IRS1 gene is hsa-miR-126-3p.1; The miRNAs associated with the PPARG gene are hsa-miR-3666, hsa-miR-130b-3p, and hsa-miR-4295; The miRNA associated with the IL13 gene is hsa-miR-101-3p.1; The miRNA associated with FGF2 gene is hsa-miR-203a-3p.2; The related miRNAs of ICAM1 gene are hsa-miR-873-5p.2 and hsa-miR-377-3p; The miRNAs associated with the HIF1A gene are hsa-miR-199a-5p and hsa-miR-199b-5p.

4. Discussion

Atherosclerosis causes serious harm to human health. Its main hazards include cardiovascular disease, peripheral artery disease, thrombosis, hypertension, increased risk of complications and death. Atherosclerosis can lead to serious complications, such as heart disease, stroke, peripheral artery disease, etc. These complications may lead to disability and increase the risk of death. Atherosclerosis is a chronic and progressive disease. If it is not intervened and treated in time, it will do great harm. The occurrence and development of atherosclerosis involve multiple molecular mechanisms. Hypertension, high cholesterol, diabetes and other risk factors can lead to endothelial cell damage. After endothelial cell injury, it will release inflammatory mediators and Cell adhesion molecule, promote the adhesion and infiltration of Monocyte and T lymphocytes,

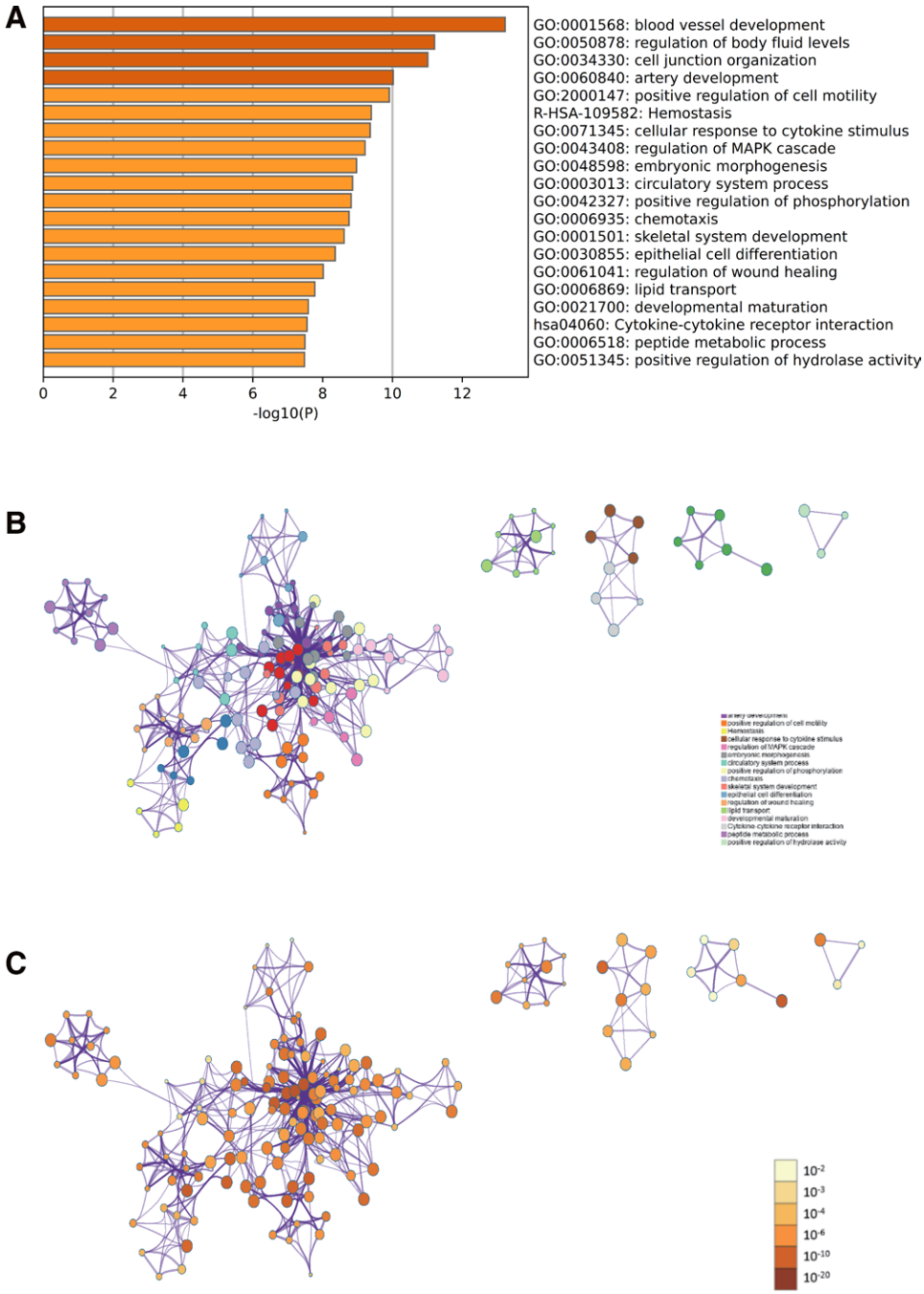

Figure 3. Metascape enrichment analysis. (A) In the enrichment project of Metascape, vascular development, regulation of body fluid levels, and positive regulation of cell motility can be seen in the GO enrichment project. (B) Output enrichment networks colored with enrichment terms. (C) Output enrichment networks colored with *P* values.

and trigger inflammatory reaction.[11–14] Low density lipoprotein cholesterol (LDL-C) is ingested, oxidized, and modified in the vascular wall of endothelial injury. Oxidized LDL can induce Monocyte to transform into macrophages, and engulf oxidized LDL to form Foam cell. Foam cell accumulate and gradually form patches.[15–18] The stability of plaque plays an important role in the progression and complications of atherosclerosis. Stable plaques have thicker fibrous caps and fewer inflammatory cells, making them relatively less prone to rupture. Unstable plaques, on the other hand, have weak fibrous caps, a large number of inflammatory cells, and a lipid rich core area, which are prone to rupture and form blood clots.[19–22] In the process of plaque formation, smooth muscle cell proliferation and collagen deposition are important tissue repair reactions. Smooth muscle cell proliferation leads to plaque enlargement and arterial wall thickening, and collagen deposition contributes to plaque stability.[23–26] When a plaque ruptures, platelets in the blood will gather at the site of the plaque rupture, forming blood clots. Thrombosis can block arteries, leading to acute vascular occlusion, leading to serious complications, such as myocardial infarction and stroke.[27,28] These molecular mechanisms interact to cause the occurrence and development of atherosclerosis. In addition to the above processes, some molecular mechanisms, such as cytokines, inflammatory mediators, growth factors, and cell apoptosis are also involved. Intervention measures, such as reducing risk factors, controlling inflammatory reaction and regulating lipid metabolism can help prevent and treat atherosclerosis.

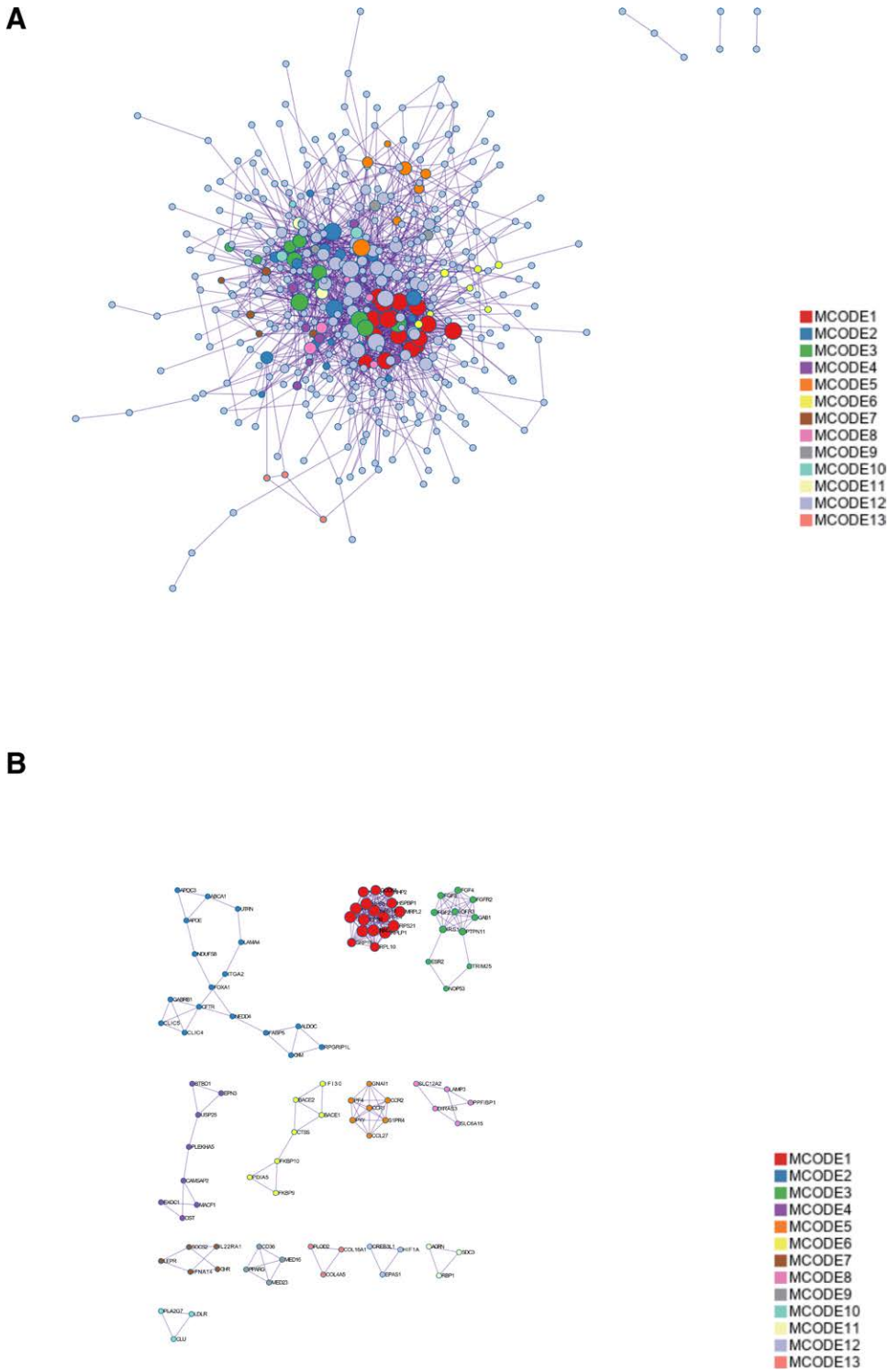

Figure 4. Metascape enrichment analysis.

It is very important to explore the molecular mechanism of atherosclerosis for the research of targeted drugs. The main result of this study is that CASP1 gene is highly expressed in atherosclerosis. The higher the CASP1 gene is, the worse the prognosis is.

CASP1 is a gene encoding Cysteine protease 1 (Caspase-1). Caspase-1 is an enzyme of the Cysteine protease family, which plays an important role in inflammation and immune response. Caspase-1 is mainly involved in the production of inflammatory cytokine and the regulation of inflammatory response. It is a cysteine specific protease, which can shear and activate a variety of cytokine precursors, including pro-inflammatory cytokine IL-1β and IL-18. These cytokines play important regulatory roles in inflammation and immune responses. Caspase-1 itself is a nonactive precursor enzyme that needs to undergo self-lysis under the activation of inflammatory signals to form an active enzyme. Once activated, Caspase-1 can cleave and activate other protease family members, forming an enzyme cascade reaction that further regulates inflammation and immune responses. Activation of

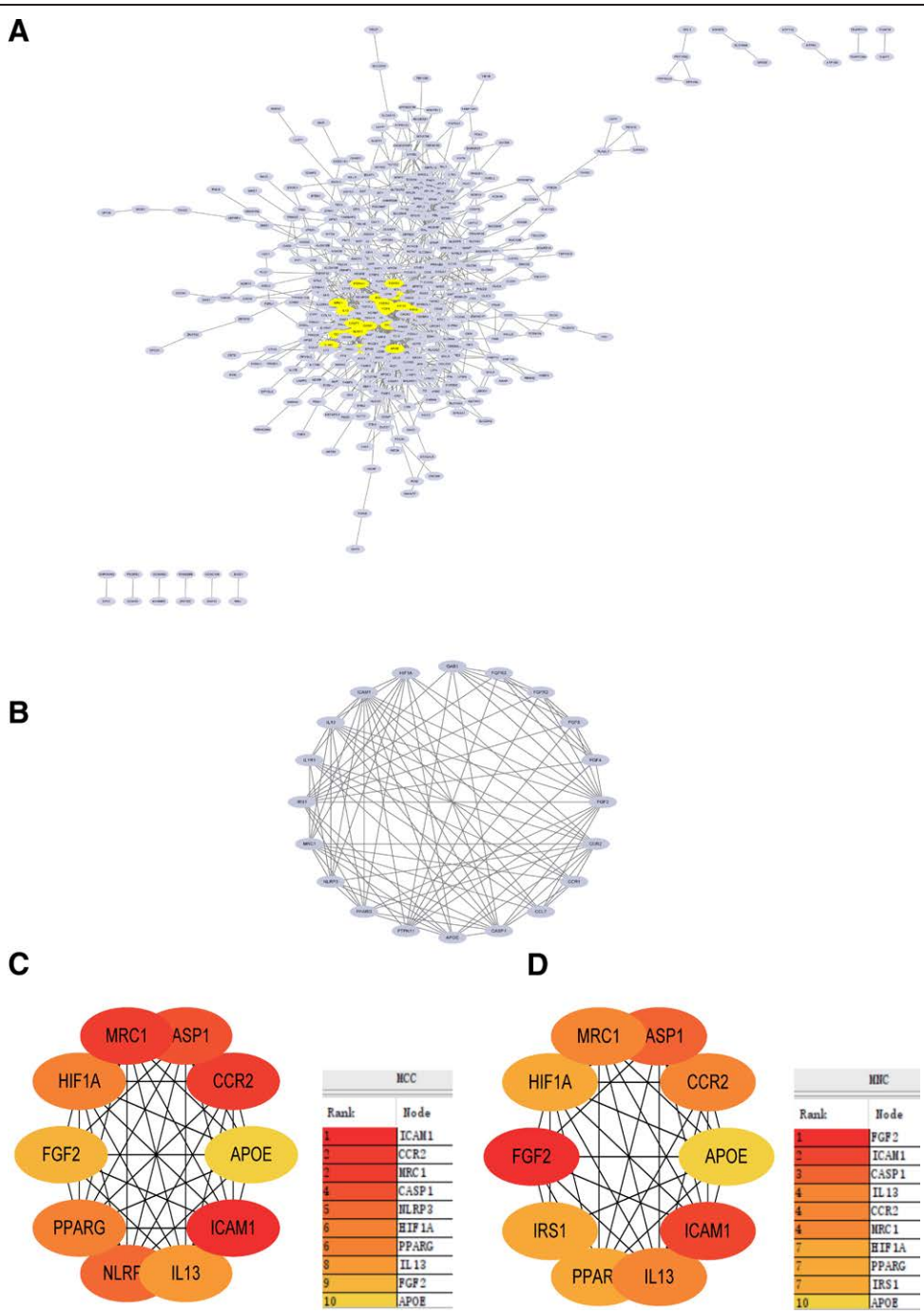

Figure 5. Construction and analysis of protein–protein interaction (PPI) network. (A) The PPI network. (B) Core gene clusters. (C) MCC was used to identify central genes. (D) MNC was used to identify central genes.

Caspase-1 and its activated Cytokine IL-1β and IL-18 plays an important role in the inflammatory response. They promote the release of inflammatory mediators, vascular dilation, white blood cell infiltration, and other inflammatory response processes. IL-1β overproduction and activation of IL-18 and IL-18 may lead to the development of inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and gout. In addition to cleaving and activating cytokines, Caspase-1 is also involved in the regulation of other cellular processes, including apoptosis, cell cycle regulation, and inflammation related cell death.[29] Some studies have shown that Caspase-1 promotes atherosclerosis by enhancing the inflammatory state of lesions, and its mechanism may involve the activation of disease-related immune cells and the expression of IFN-γ.[30] Therefore, it is speculated that CASP1 gene may play an important role in the inflammatory response of atherosclerosis. The above literature review is consistent with our results. CASP1 gene is highly expressed in atherosclerosis. The higher the CASP1 gene, the worse the prognosis.

Although this article has conducted rigorous bioinformatics analysis, there are still some shortcomings. This study did not conduct animal experiments on gene overexpression or knockout to further validate its function. Therefore, in future research, we should conduct in-depth exploration in this area.

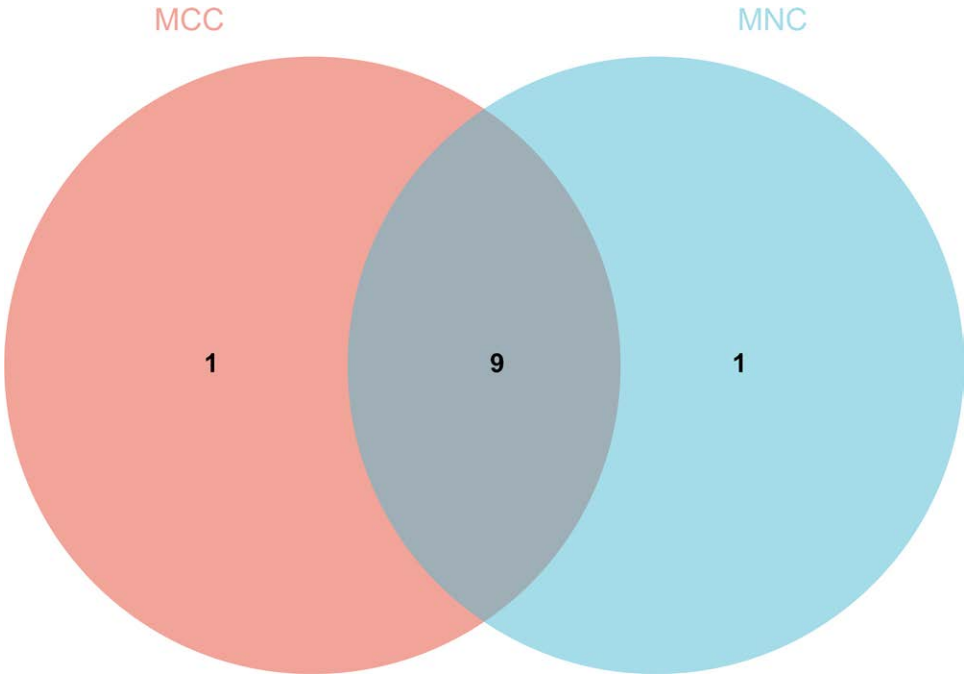

Figure 6. The intersection was obtained using Wayne plots, and the union was obtained using Excel.

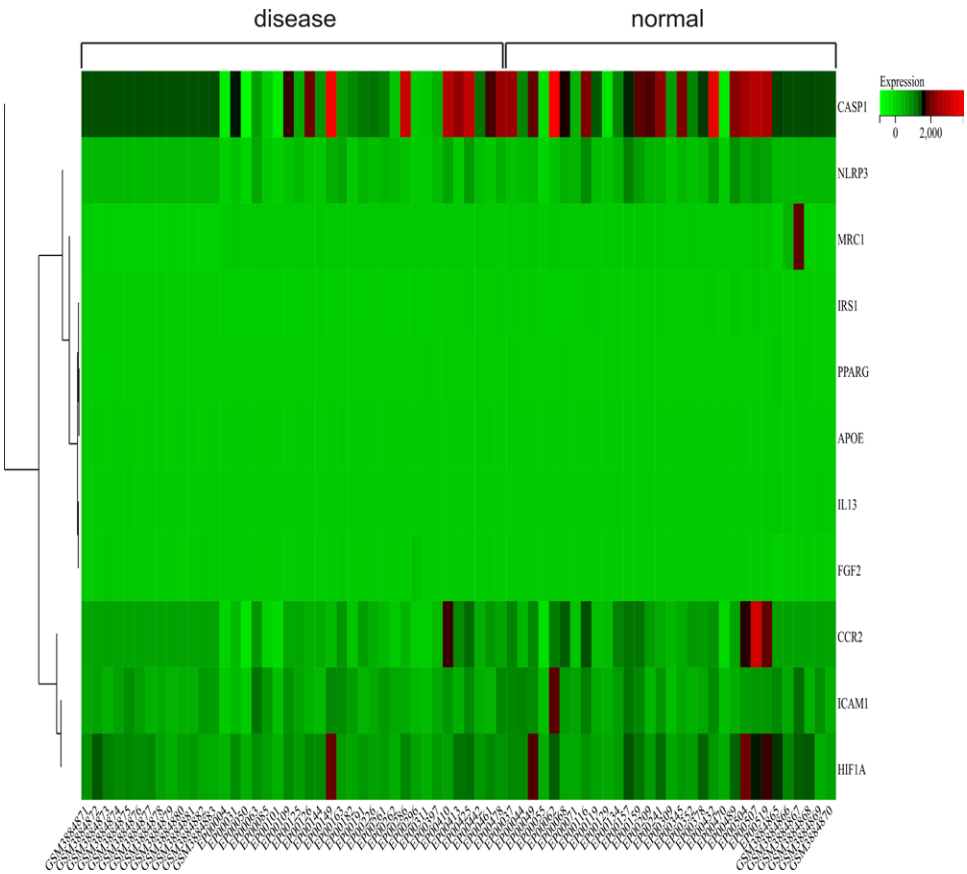

Figure 7. Gene expression heatmap. The calorimetry of core gene expression in samples was visualized.

5. Conclusion

CASP1 is highly expressed in atherosclerosis, and may play a significant role in the development of atherosclerosis through cell regulation and other pathways. CASP1 may serve as a molecular target for precise treatment of atherosclerosis, providing a certain direction basis for the mechanism research of atherosclerosis. Future research directions will further expand the understanding of the function and

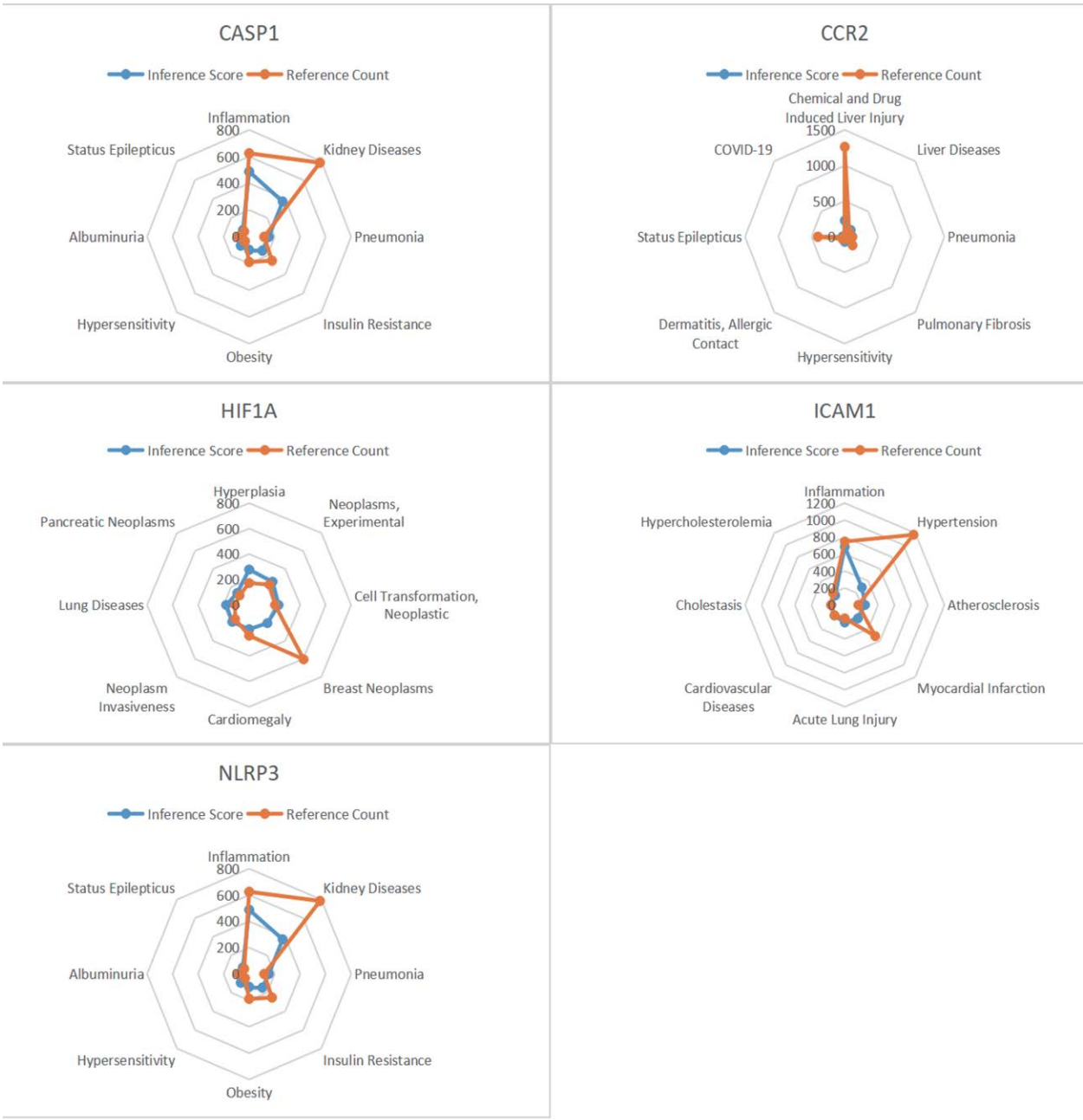

Figure 8. CTD analysis. Five genes (CASP1, NLRP3, CCR2, ICAM1, HIF1A) were found to be associated with pneumonia, inflammation, cardiac enlargement, and tumor invasiveness.

regulatory mechanism of CASP1, as well as its exact role in atherosclerosis. Exploring the molecular mechanism of CASP1 in atherosclerosis and understanding that CASP1 is involved in the regulation of inflammation, apoptosis, or other related biological processes could provide a deeper understanding for the development of new therapeutic strategies. Based on the in-depth understanding of CASP1, attempts are made to develop therapeutic strategies against CASP1. This may include small molecule drugs, antibodies, or other therapeutic means to modulate CASP1 expression or activity to slow or prevent the development of atherosclerosis. A larger sample size study on the relationship between CASP1 and clinical characteristics, disease progression and prognosis of patients will help to determine the potential use of CASP1 in therapeutic strategies and the clinical value of therapeutic targets, and provide more information for individualized treatment.

Author contributions

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Writing—review & editing: Yongchao Li, Lihong Du.
Validation: Lihong Du.
Visualization: Lihong Du.

Table 1

A summary of miRNAs that regulate hub genes.

	Gene	miRNA
1	CASP1	None
2	NLRP3	hsa-miR-223-3p
3	MRC1	hsa-miR-23c hsa-miR-130a-5p hsa-miR-23a-3p
4	IRS1	hsa-miR-126-3p.1
5	PPARG	hsa-miR-3666 hsa-miR-130b-3p hsa-miR-4295
6	APOE	None
7	IL13	hsa-miR-101-3p.1
8	FGF2	hsa-miR-203a-3p.2
9	CCR2	None
10	ICAM1	hsa-miR-873-5p.2 hsa-miR-377-3p
11	HIF1A	hsa-miR-199a-5p hsa-miR-199b-5p

Data curation: Lingbing Meng, Chao Lv, Xinping Tian.
Formal analysis: Lingbing Meng, Chao Lv, Xinping Tian.
Methodology: Lingbing Meng, Chao Lv, Xinping Tian.

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