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Genetic targets related to aging for the treatment of coronary artery disease

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Abstract

Background Coronary Artery Disease (CAD) is the most common cardiovascular disease worldwide, threatening human health, quality of life and longevity. Aging is a dominant risk factor for CAD. This study aims to investigate the potential mechanisms of aging-related genes and CAD, and to make molecular drug predictions that will contribute to the diagnosis and treatment.

Methods We downloaded the gene expression profile of circulating leukocytes in CAD patients (GSE12288) from Gene Expression Omnibus database, obtained differentially expressed aging genes through "limma" package and GenaCards database, and tested their biological functions. Further screening of aging related characteristic genes (ARCGs) using least absolute shrinkage and selection operator and random forest, generating nomogram charts and ROC curves for evaluating diagnostic efficacy. Immune cells were estimated by ssGSEA, and then combine ARCGs with immune cells and clinical indicators based on Pearson correlation analysis. Unsupervised cluster analysis was used to construct molecular clusters based on ARCGs and to assess functional characteristics between clusters. The DSigDB database was employed to explore the potential targeted drugs of ARCGs, and the molecular docking was carried out through Autodock Vina. Finally, single-cell data (GSE159677) of arterial intima was used to further explore the expression of aging signature genes in different cell subpopulations.

Results We identified 8 ARCGs associated with CAD, in which HIF1A and FGFR3 were up while NOX4, TCF7L2, HK3, CDK18, TFAP4, and ITPK1 were down in CAD patients. Based on this, CAD patients can be divided into two molecular clusters, among which cluster A mainly involves functional pathways such as ECM receptor interaction and focal adhesion; cluster B mainly involves functional pathways such as amimo sugar and nucleotide sugar metabolism and pyrimidine metabolism. In addition, the molecular docking results showed that retinoic acid and resveratrol had good binding affinity with targets genes. Further single-cell analysis results showed that NOX4, TCF7L2, ITPK1, and HIF1A were specifically expressed in different types of cells in atherosclerotic tissues.

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Conclusion Our study identified several ARCGs that may be involved in the pathogenesis and progression of CAD. Further, retinoic acid and resveratrol were potential candidate molecule drugs for inhibiting these targets.

Keywords Coronary artery disease, Aging-related genes, Machine-learning strategy, Molecular Docking, Single-cell sequencing

Introduction

Coronary artery disease (CAD) is a cardiovascular disease caused by coronary atherosclerosis, which is characterized by stable angina, unstable angina, myocardial infarction, and sudden cardiac death [1]. In 2022, there were 315 million prevalent cases of CAD globally and the aged-standardized prevalence was 3.6% [2]. There are many risk factors for CAD, such as genetics, environmental factors, and lifestyle, which have a certain impact on the occurrence and development of the disease [3]. Although pharmacological treatment and vascular reconstruction therapy have to some extent reduced the mortality rate and improved the quality of life of CAD patients, it remains the main disease that endangers human life and health [4, 5]. Therefore, exploring the influencing factors and pathogenesis is important for the prevention and treatment of CAD.

Aging is the core manifestation of various diseases (e.g., cardiovascular diseases, neurodegenerative diseases, etc.) and affects many cells, tissues, and organs in the body [6]. Aging of cardiovascular system is a key factor in the occurrence and development of CAD [7], involving changes in epigenetics, intercellular communication, chronic inflammation, and ecological imbalance [8]. Previous studies have shown that the expression and modification of key aging genes such as APOE, FOXO1, and IGF-1 are closely related to multiple stages of CAD [9, 10]. In addition, oxidative stress and circulating inflammation will lead to accelerated aging of cardiomyocytes and even extensive DNA damage [11]. However, there have been limited studies examining the relationship between aging-related genes and immune infiltrations in CAD thus far.

With the rapid development of microarray and high-throughput sequencing technologies, more and more CAD related genetic data are being uploaded into Gene Expression Omnibus (GEO) databases, providing opportunities for further bioinformatics data mining as well as for recognizing CAD-related genetic changes. However, one of the key challenges in data processing is dealing with the feature dimensionality and redundancy of the data [12]. To address this issue, machine learning is increasingly being used to identify feature selection classifiers and to build robust diagnostic or prognostic prediction models for different diseases [13]. For example, Wang et al. identified immune cell infiltration and diagnostic biomarkers in unstable atherosclerotic plaques through machine learning [14]. Based on this, the cross-combination of machine learning may help in bioinformatics data mining and analysis of CAD related aging genes.

The search for pathways that can intervene in the aging process and extend healthy lifespans is a key aspect of aging research. Although some molecule drugs have shown objective effects of delaying aging in model animals, their targets are still unclear [6, 15, 16]. Molecular docking is often used to elucidate the interactions between molecules in depth and has important applications in drug development [17]. In this study, we screened CAD associated aging related characteristic genes (ARCGs) by machine learning and constructed different aging clusters of CAD. Moreover, we explored molecular drugs related to ARCGs and verified their feasibility by molecular docking, in order to provide new insights into the pathogenesis and effective treatment of CAD.

Materials and methods

Data download and preprocessing

The raw gene expression profiles of CAD patients come from GSE12288 [18] and GSE159677 [19] datasets of the GEO (https://www.ncbi.nlm.nih.gov/gds/). The GSE12288 dataset includes of circulating leukocyte specimens from 110 CAD patients (CAD index > 23) and 112 non-CAD controls (CAD index = 0), evaluated for gene expression using the Affymetrix U133A chips. The GSE159677 dataset contains single cell RNA sequencing (scRNA-seq) of arterial intima in 3 patients with atherosclerosis, which were sequenced by Illumina NextSeq 500. A total of 497 aging related genes were obtained from GeneCards (https://www.genecards.org/) and Human Aging Genomic Resources (https://genomics.senescence.info/). There were 338 aging genes from GeneCards, and the criteria were aging-related protein-coding genes with a score ≥ 10. The Human Aging Genomic Resources are mainly 307 Human Ageing-Associated genes.

Differential aging genes and functional analysis

In R (4.3.0), we screened differentially expressed genes in CAD and healthy control (HC) populations using "limma" package with $P < 0.05$ as the standard. Subsequently, we intersected them with aging related genes by Venn plots, resulting in aging related differential genes (ARDGs), which were displayed by heatmap. Based on the " clusterProfiler " package [20], the potential biological and functional attributes of ARDGs were investigated

through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses.

Machine learning for discovery of ARCGs

To further screen characteristic genes, two machine learning algorithms, least absolute shrinkage and selection operator (LASSO) and random forest (RF), were applied. LASSO, a dimension reduction approach, was found to be superior to regression analysis for evaluating high-dimensional data. The LASSO analysis involved implementing a 10-fold cross-verification via the "glmnet" package [21], using to determine the optimal lambda value. Partial likelihood bias was minimized to prevent overfitting of the regression model. On the other hand, RF elimination in RF algorithms was a supervised machine learning method used to sort CAD related ARCGs, with relative importance > 0.3 identified as feature genes. Finally, in order to validate the clinical application and usability of risk characteristics based on ARCGs, nomogram charts and receiver operating characteristic (ROC) curves were utilized.

Correlation analysis of ARCGs with immune cells and clinical features

The abundance and difference results of 22 immune cells between the CAD and HC groups were assessed based on the inverse convolution algorithm using the source code and benchmark database files officially provided by CIBERSORT [22]. In addition, Pearson correlation analysis was also used to determine the correlation between ARCGs, immune cells, and clinical features, which was visualized through correlation heatmaps. $P < 0.05$ is considered statistically significant.

Constructing aging clusters of CAD based on ARCGs

The ARCGs expression matrices of 110 CAD patients were extracted and grouped by an unsupervised cluster analysis algorithm to accurately identify CAD patients with common genetic characteristics. Among them, ConsensusClusterPlus is an unsupervised classification method extended with R language, including item tracking, item consensus, and generation of clustered consensus maps [23]. Briefly, the covariance coefficients and the shear values of the best clusters were obtained by passing the homologous gene matrices to the consensus clustering algorithm (input parameters k = 2–10). After obtaining the optimal shear values and clusters, the expression of ARCGs in clusters was displayed in the form of heatmap. Principal component analysis (PCA) was used to show the difference and distinction between different aging clusters of CAD.

Functional analysis of aging clusters of CAD

To explore the functional differences between aging clusters of CAD, we introduced differential genes ($|\log_2 FC| > 0.5$, $P < 0.05$) from the clusters into Metascape (https://metascape.org/) for biological function enrichment analysis [24]. Subsequently, the pathways with higher enrichment were clustered and networks were constructed based on functional relevance. Moreover, the "clusterProfiler" package was utilized for Gene Set Enrichment Analysis (GSEA) to identify the potential mechanisms of c2 (c2.cp.kegg.v7.5.1.entrez.gmt) in molecular signature database.

Screening and molecular Docking of molecule drugs

The Drug Characteristic Database (DSigDB, http://dsigdb.tanlab.org/DSigDBv1.0/) is a new gene set resource that associates drugs/compounds and their target genes [25]. We imported CAD related ARCGs into DSigDB to obtain potential target drugs. The 3D structure of the ARCGs target protein was downloaded from the RCSB Protein Data Bank (RCSB PDB, http://www.pdb.org/). The mod ified versions of the protein, as well as the ligand, were separated and the water was removed using the Pymol software. Additionally, the 3D structure of the drugs component was obtained from PubChem, and hydrogen was added and charges were calculated. Subsequently, Autodock Vina 1.2.2 software was utilized to perform docking simulations with the core target protein, while limiting the binding energy to be ≤ -5.0 kcal·mol^{-1} in order to identify stable binding sites.

ScRNA-seq to explore expression of ARCGs

ScRNA-seq to explore expression of ARCGs raw data from 3 CAD patients were read through the "Seurat" package [26]. Cells with < 500 or > 5000 genes were excluded as non-cellular or cellular aggregates. In addition, cells with a certain percentage of mitochondrial or ribosomal genes > 10% or 5%, respectively, were also filtered out. Then, single cell data were integrated through "Harmony" package and the top 2000 highly expressed cells were included in subsequent analysis. PCA was used to divide clusters by linear relationships and cluster trees were used to visualize relationships between clusters at multiple resolutions. Integrate and annotate different clusters obtained from PCA using "SingleR" package [27]. Further dimensionality reduction and display were achieved through t-distribution random neighborhood embedding (t-SNE) and unified manifold approximation and projection (UMAP) algorithms. Finally, the expression of ARCGs was shown in cellular clusters.

Results

Identification and functional analysis of CAD related ARDGs

The GSE12288 data were normalized and differential genes were extracted using the "limma" package. According to the screening criteria of $P < 0.05$, a total of 924 differentially expressed genes were obtained. As shown in Fig. 1A and 37 ARDGs were obtained after intersecting with 497 aging genes (Table S1). Specific expression of each gene of ARDGs in the CAD and HC groups was shown as the heatmap (Fig. 1B). Next, the functional pathways involved in ARDGs were initially explored by GO and KEGG enrichment analyses. In GO terms, cellular response to stress, cell death, programmed cell death, apoptotic process, and phosphorylation were mainly enriched (Fig. 1C). In KEGG analyses, PI3K-Akt signaling pathway, HIF-1 signaling pathway, Wnt signaling pathway, and MAPK signaling pathway were mainly enriched (Fig. 1D).

Selection of CAD related ARCGs by machine learning

Two machine learning algorithms were applied to select characteristic genes associated with CAD and aging genes. In LASSO regression algorithm, 29 genes from the 37 ARDGs were identified as potential diagnostic biomarkers (Fig. 2 A and B). In RF algorithm, the top 10 genes with relative importance > 0.3 were identified as potential diagnostic biomarkers (Fig. 2C and D). Then, 8 genes (HK3, CDK18, TFAP4, FGFR3, ITPK1, HIF1A, TCF7L2, and NOX4) were overlapped via Venn diagram (Figure S1A), and served as CAD related ARCGs. In addition, chromosomes and positions of the 8 genes were displayed in circle diagram (Figure S1B). Columnar line graphs were constructed to diagnose CAD by integrating ARCGs and the total score was obtained by summing the scores of all trait genes (Figure S2A). Moreover, when the ARCGs were integrated into one variable, the AUC of the ROC curve was 0.761 (Figure S2B). This indicated that the ARCGs have good diagnostic efficiency in predicting CAD.

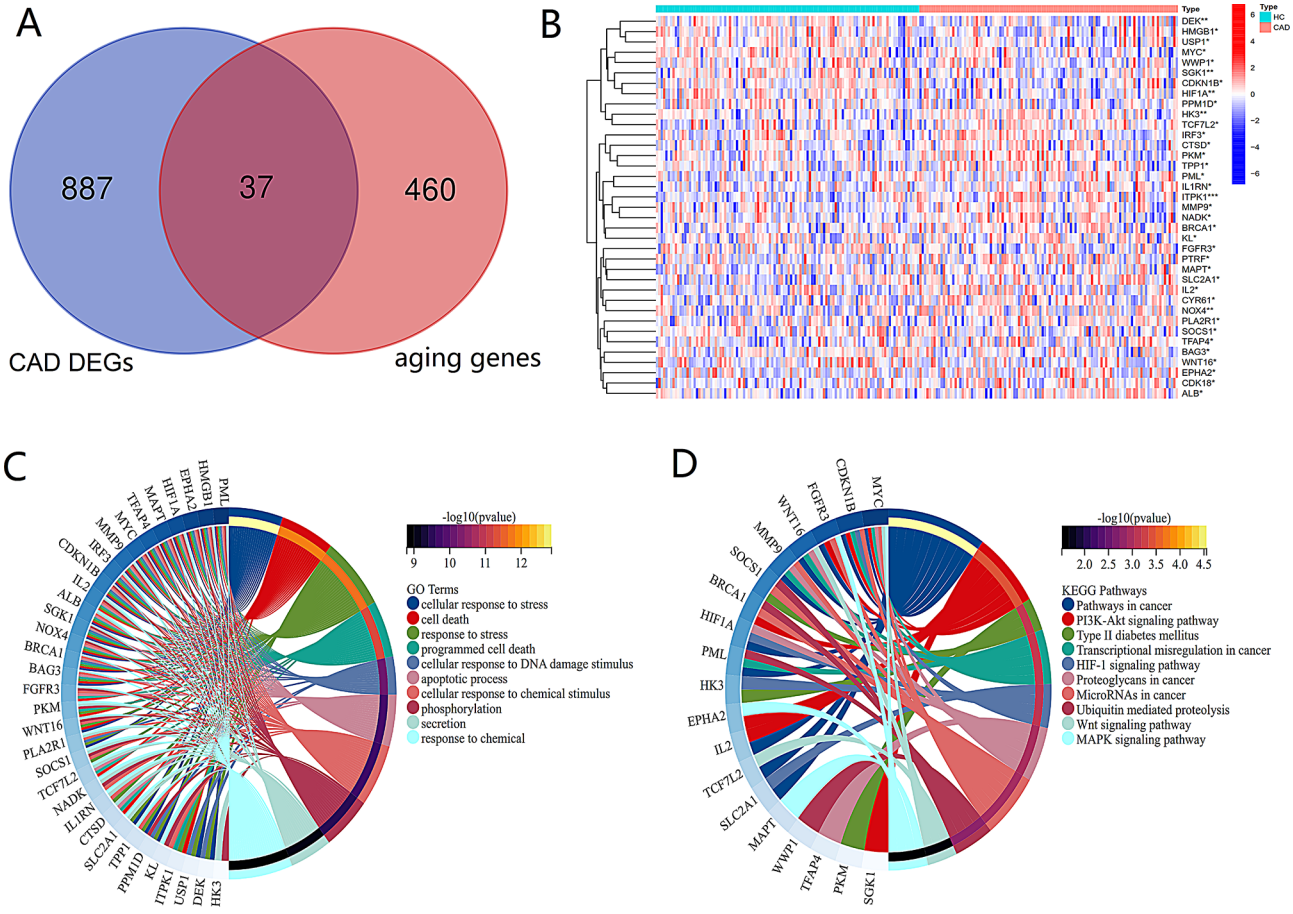

Fig. 1 Identification and functional analysis of CAD related ARDGs. (**A**) Venn diagram obtained CAD related ARDGs from CAD DEGs and aging genes. (**B**) Heatmap displays the expression of ARDGs in CAD c and HC groups. (**C**) GO enrichment analysis of ARDGs. (**D**) KEGG enrichment analysis of ARDGs

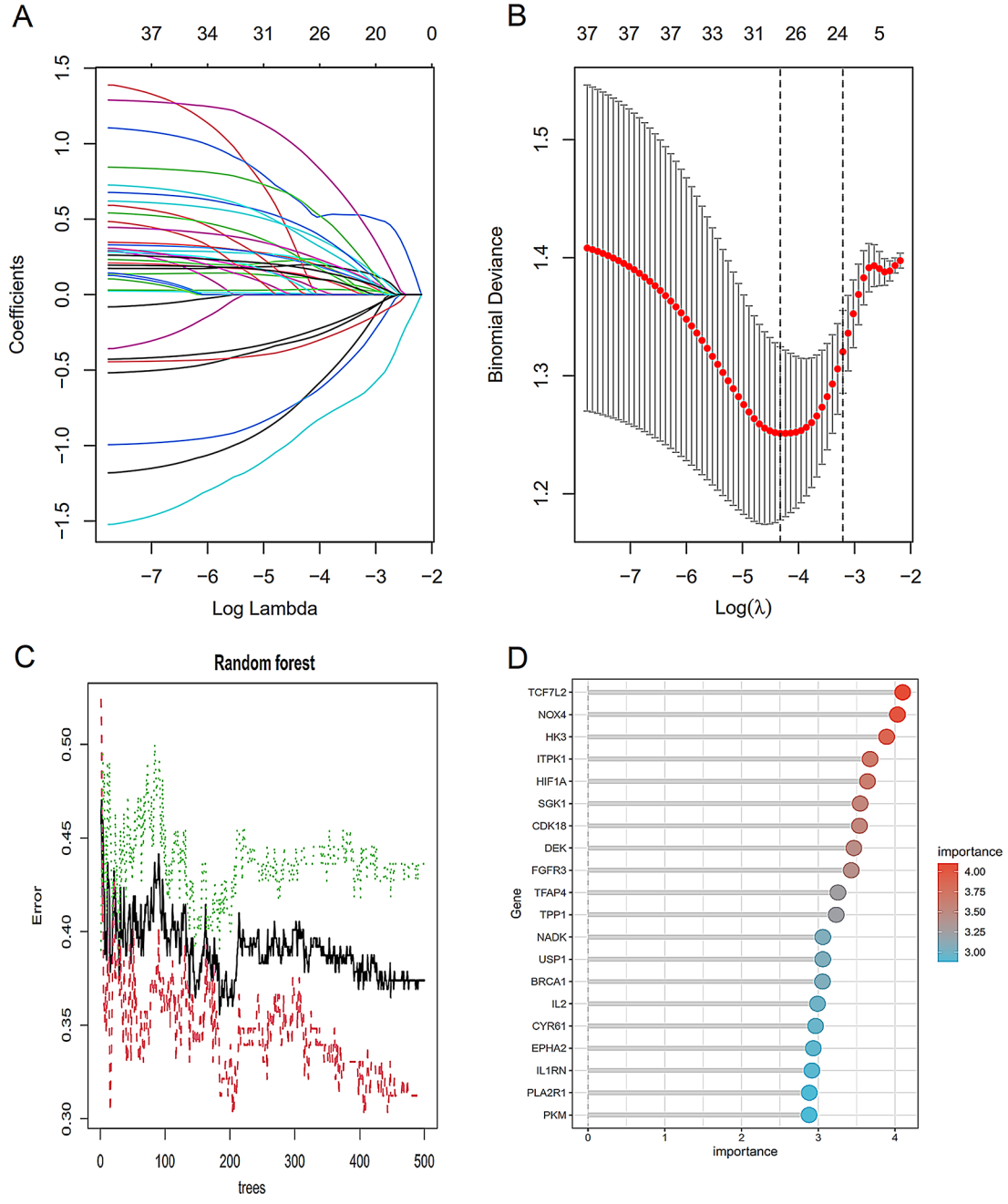

Fig. 2 Machine learning screening of characteristic genes associated with CAD and aging genes. (**A**) Profiles of the LASSO regression coefficients. (**B**) Tuning feature selection in the LASSO model. (**C**) The error rate confidence intervals for RF model. (**D**) The relative importance of genes based on cross-validation error rate curves

Correlation of ARCGs with immune cells and clinical features

The CIBERSORT algorithm is used to evaluate the immune cells infiltration patterns of CAD and HC groups. The results showed that the expression of T cells CD4 naïve was significantly reduced in CAD patients, while the expression of Macrophages M0 was significantly increased (Fig. 3A). Then, through Pearson correlation analysis between ARCGs and immune cells, we found that (Fig. 3B) ITPK1 was significantly positively correlated with Macrophages M0 and Neutrophils, while negatively correlated with T cells CD4 naïve and Macrophages M2; NOX4 was significantly positively correlated with T cells CD4 memory activated and negatively correlated with T cells CD4 naïve; HK3 was significantly positively correlated with Monocytes and negatively correlated with T cells CD8; HIF1A was significantly positively correlated with Neutrophils and Macrophages M2,

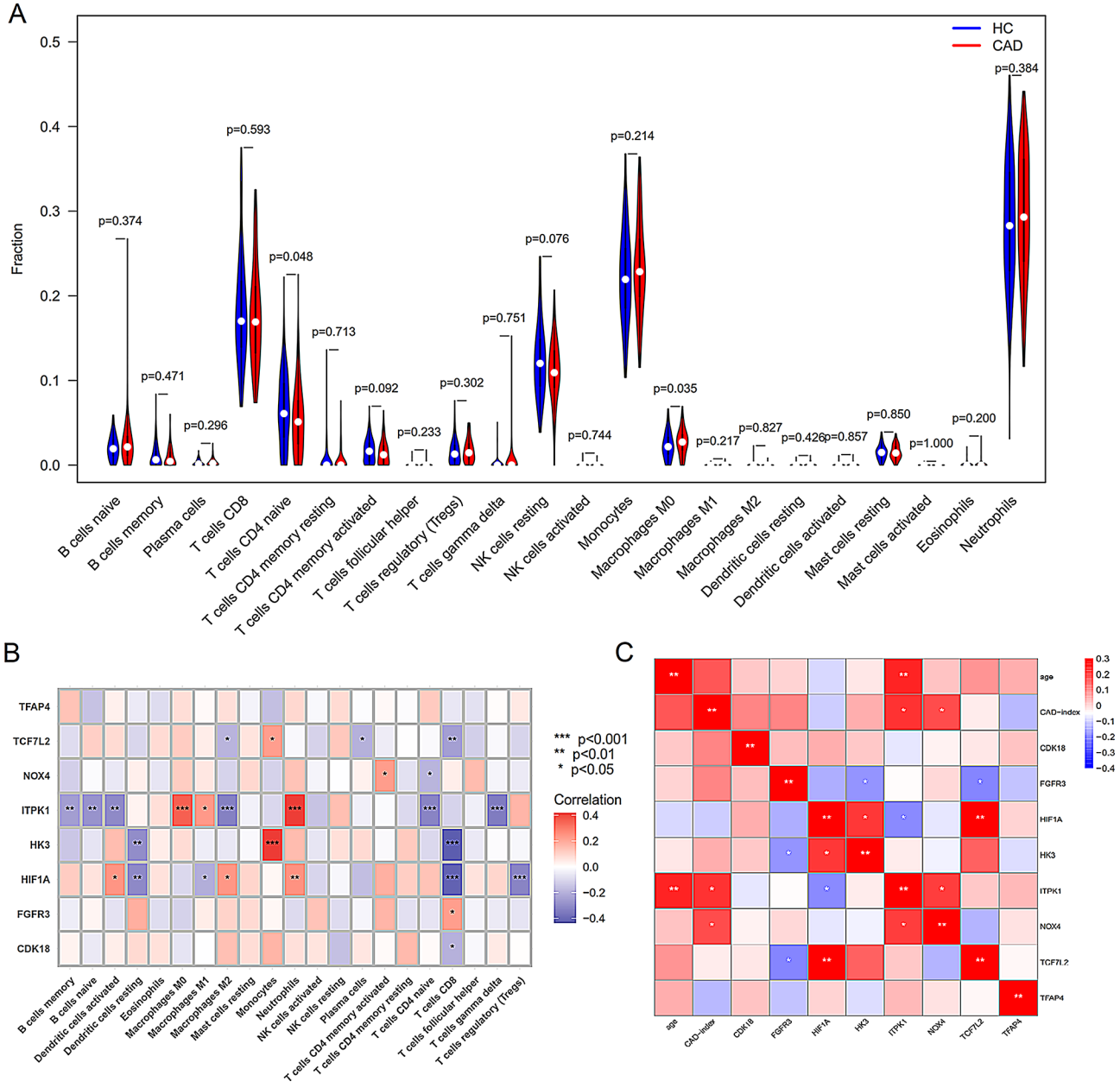

Fig. 3 Correlation of ARCGs with Immune Cells and Clinical Features. (**A**) Differences in 22 immune cells. composition between the CAD and HC groups. (**B**) Correlation map of ARCGs and immune cells. (**C**) Correlation map of ARCGs and Clinical Features

while negatively correlated with T cells CD8 and Tregs. On the other hand, the Pearson correlation analysis between ARCGs and clinical features showed the expression of ITPK1 and NOX4 was significantly positively correlated with CAD-index, and ITPK1 was also significantly positively correlated with age (Fig. 3C).

Constructing CAD aging models based on ARCGs

Based on the expression of the 8 ARCGs (HK3, CDK18, TFAP4, FGFR3, ITPK1, HIF1A, TCF7L2, and NOX4), we clustered the 110 CAD patients into aging clusters A and B by consensus cluster analysis (Fig. 4A), and detailed ARCGs expression information in 2 aging clusters was presented in heatmap (Fig. 4B). In addition, PCA showed good discrimination between the aging clusters A and B (Fig. 4C).

Differences in functional features between two models

Using$|\log_2 FC| > 0.5$ and $P < 0.05$ as the screening criteria, we identified 64 differentially expressed genes between the 2 clusters. Through Metascape database, we found that these differential gene introductions are mainly enriched in anion transport, voltage gated potassium channels cell-cell adhesion, and tissue homeostasis

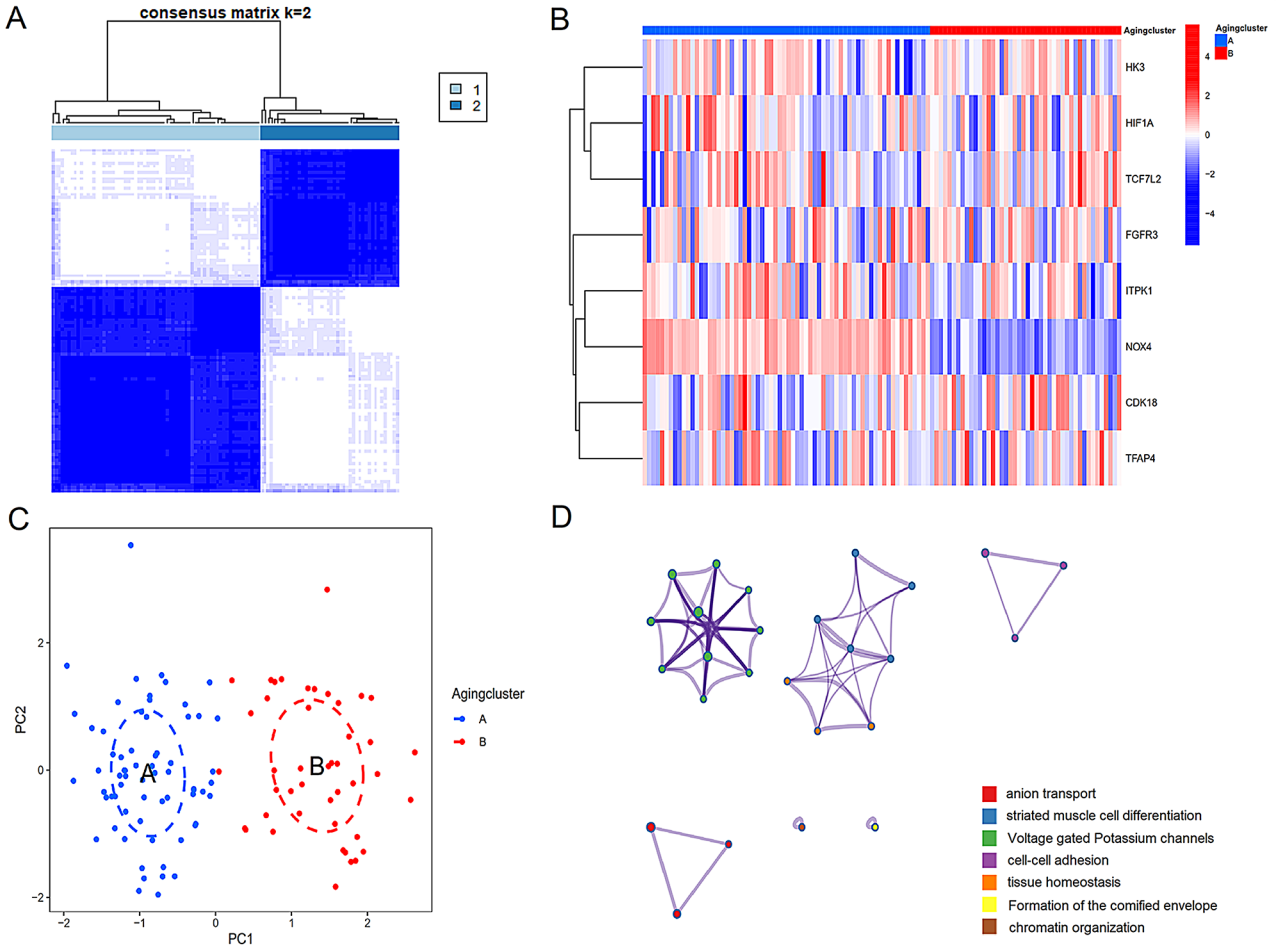

Fig. 4 Constructing CAD Aging Models Based on ARCGs. (**A**) Consensus clustering matrix for k = 2. (**B**) Heatmap displays the expression of ARCGs in cluster A and B. (**C**) PCA displays the differentiation between cluster A and B. (**D**) Exploring the functional pathways involved in differential denes in cluster A and B based on Metascape

(Fig. 4D). In addition, we further evaluated the critical functional pathways of cluster A or B. The results of GSEA revealed that the ECM receptor interaction, focal adhesion, and Glycosphingolipid biosynthesis ganglio series were upregulated in aging cluster A (Fig. 5A-C), while the amimo sugar and nucleotide sugar metabolism, intestinal immune network for IGA production, and pyrimidine metabolism were upregulated in aging cluster B (Fig. 5D-F).

Screening and molecular Docking validation of molecule drugs

To explore the candidate Molecule drugs for CAD, we considered 8 ARCGs as drug targets and used DSigDB database for drug prediction. We screened the top 20 drugs by adjusted *P*-value and combined score, including 4-Hydroxytamoxifen, N-Acetyl-L-cysteine, resveratrol, retinoic acid, arsenenous acid, AZD4547 LINCS, BIBF-1120 (derivative), erythorbic acid, D-glucose, etc. (Table S2). In addition, we selected retinoic acid and resveratrol for molecular docking with their target genes by Autodock Vina. Binding energies of HIF1A with resveratrol was −6.1 kcal/mol (Fig. 6A). Binding energies of FGFR3, HIF1A, and HK3 with retinoic acid were −7.0 kcal/mol, −5.9 kcal/mol, and −7.4 kcal/mol (Fig. 6B-D). In summary, retinoic acid and resveratrol have the potential to become therapeutic drugs for CAD and may play roles through ARCGs.

Expression of ARCGs in single cells by ScRNA-seq analysis

Through the "Harmony" package, we successfully integrated three CAD single cells samples and selected the first 2000 highly expressed cells for subsequent analysis (Figure S3A and B). According to resolution = 1.5 (Figure S3C), we got 32 clusters and showed them by t-SNE and UMAP (Figure S3D and E). Afterwards, the different clusters were integrated and annotated based on maker genes by "SingleR" package, resulting in 8 cell subpopulations, namely T cells, monocyte, smooth muscle cells, macrophage, endothelial cells, tissue stem cells, NK cells

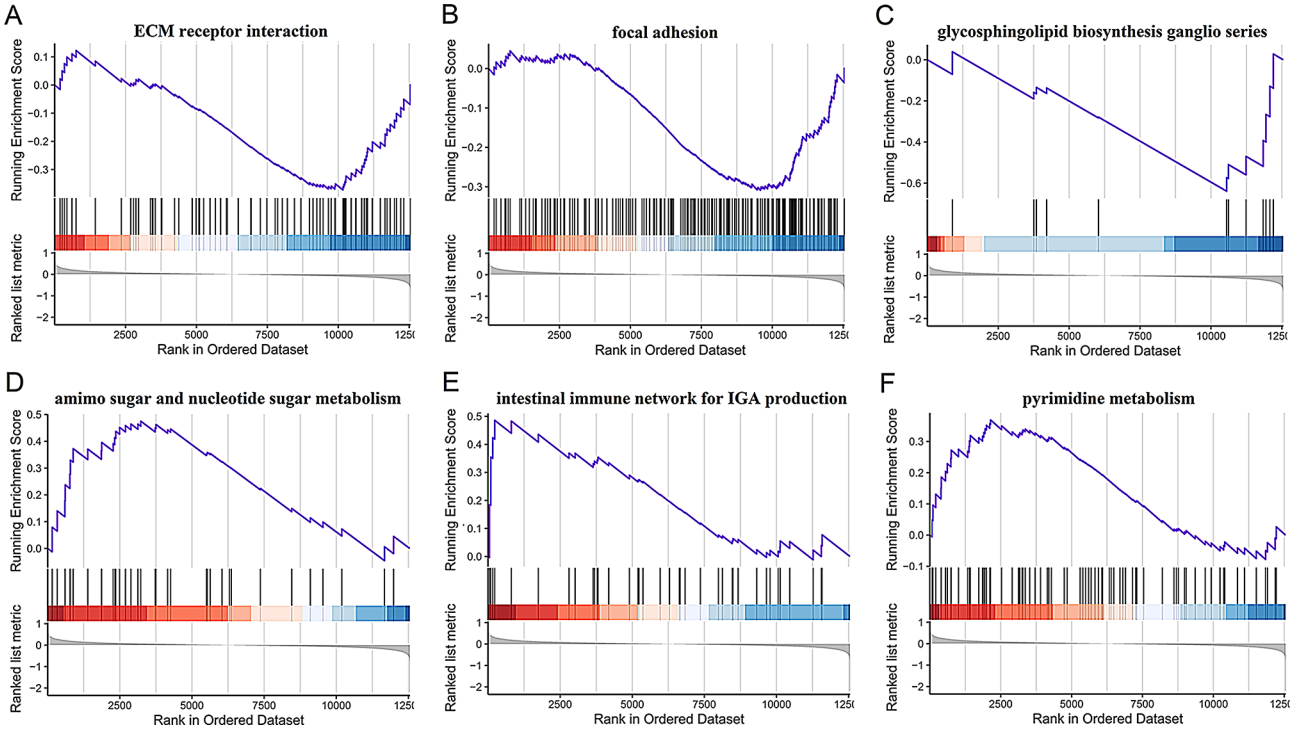

Fig. 5 Evaluating the specific functional pathways of cluster A and B through GSEA. (**A**-**C**) The ECM receptor interaction, focal adhesion, and Glycosphingolipid biosynthesis ganglio series are upregulated in aging cluster A. (**D**-**F**) The amimo sugar and nucleotide sugar metabolism, intestinal immune network for IGA production, and pyrimidine metabolism are upregulated in aging cluster B

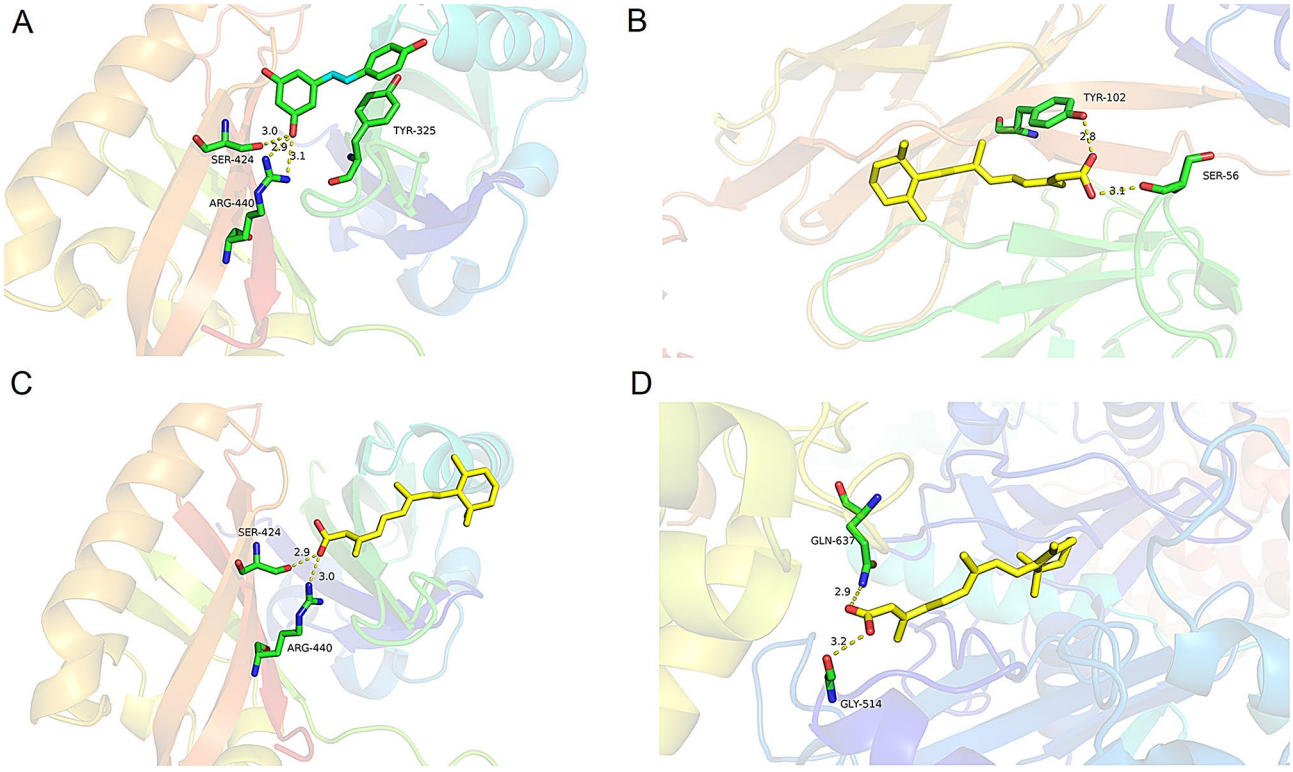

Fig. 6 Molecular docking diagram of molecule drugs and target genes. (**A**) resveratrol-HIF1A (**B**) retinoic acid-FGFR3 (**C**) retinoic acid- HIF1A (**D**) retinoic acid- HK3

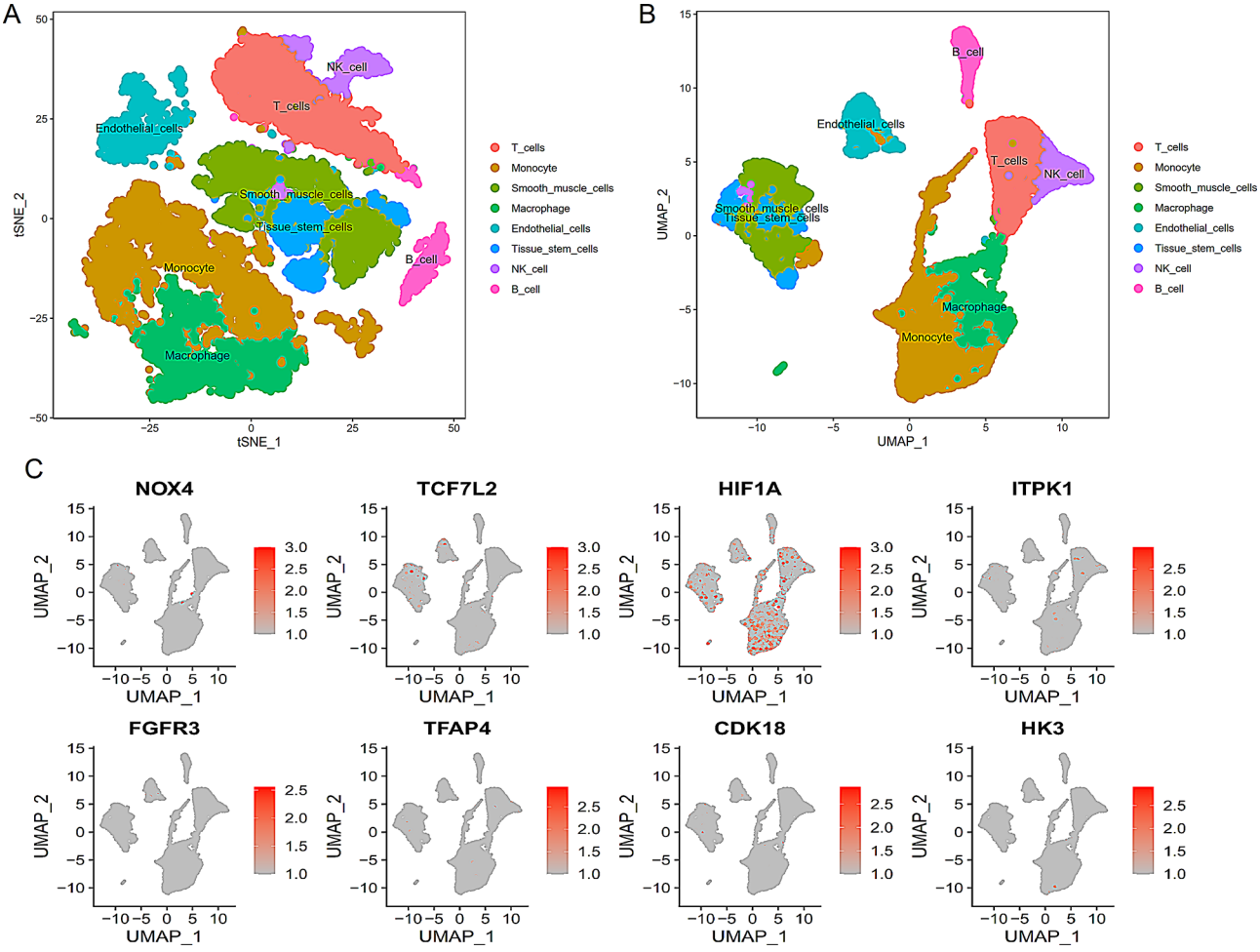

Fig. 7 Expression of ARCGs in Single Cells. (**A**) The t-SNE algorithm integrated and annotated the clusters into 8 cell subpopulations. (**B**) The UMAP algorithm integrated and annotated the clusters into 8 cell subpopulations. (**C**) The expression percentage of ARCG in each cell subgroup is shown in the UMAP diagram

and B cells (Fig. 7A-B). The percentage of expression of ARCGs in each cell subpopulations were as UMAP plots (Fig. 7C). Among them, NOX4 was mainly expressed in macrophage; TCF7L2 was mainly expressed in smooth muscle cells; HIF1A was mainly expressed in all cell subpopulations; ITPK1 was mainly expressed in T cells and monocyte.

Discussion

CAD is a serious worldwide disease and its incidence rate and prevalence is closely related to age [28]. Recently, following numerous high-throughput sequencing genetic analyzes, some important aging-associated molecules have been identified [29]. However, aging-related changes in the cardiovascular system are difficult to attribute to a single molecular mechanism. Based on the transcriptome of CAD, we mined 8 ARCGs out of 37ARDGs by machine learning. In addition, we employed various analyses such as immune infiltration, GSEA, and unsupervised cluster to comprehensively understand the mechanism of aging participating in CAD. Finally, molecular docking was used to explore potential therapeutic drugs (retinoic acid and resveratrol) in order to provide new insights for treatment.

A total of 37ARDGs were employed for functional enrichment analysis. Cellular response to stress, cell death, apoptotic process, and phosphorylation were mainly enriched in GO analysis. PI3K-Akt signaling pathway, HIF-1 signaling pathway, and MAPK signaling pathway were mainly enriched in KEGG analysis. The aging state is accompanied by inability to respond to endogenous and exogenous stimuli, enhanced secretion phenotype, and resistance to cell death [30]. Furthermore, phosphorylation is widely associated with cell death, amplifying the effects of cell-intrinsic proliferative arrest and contributing to impaired tissue regeneration, organ aging, and chronic age-related diseases [8]. Similarly, dysfunction of mitochondrial oxidative phosphorylation leads to oxidative damage caused by ROS production, which is an important molecular basis for the

pathological and physiological conditions of aging [31]. Kim et al. found that the HIF-1 pathway can improve cell aging by inhibiting aging marker (AIMP3) and enhancing autophagy activity [32]. The PI3K-Akt pathway and MAPK pathway are common growth factor and mitogen dependent signaling pathways. Activation of the PI3K-Akt pathway has been observed in some animal models of cardiovascular disease and aging [33]. In addition, the PI3K-Akt pathway and MAPK pathway can regulate the key complexes mTOR1 and mTOR2 of the mTOR pathway [34]. Meanwhile, the mTOR complex regulates various downstream processes through phosphorylation, including lipid metabolism, protein synthesis, autophagy, and cell growth [35].

Early identification and intervention of CAD can effectively delay the progression of disease or avoid the occurrence of cardiovascular events. In this study, we further identified 8 ARCGs (NOX4, TCF7L2, HIF1A, HK3, CDK18, TFAP4, FGFR3, and ITPK1) through machine learning, and the joint prediction AUC of the model was 0.761. Moreover, further correlation analysis showed that NOX4 and ITPK1 were associated with CAD-index, and ITPK1 was positively correlated with age. NOX4 is an important effector of oxidative stress and involved in regulation of ROS [36]. Lee et al. found that NOX4 mRNA and protein expression is elevated in the aging aorta and its involvement in aging-related vascular dysfunction is associated with ROS accumulation and IRE1α phosphorylation [37]. Besides, A prospective cohort study involving 15,434 middle-aged and elderly Chinese population found that NOX4 gene mutations may be associated with risk of CAD morbidity and mortality [38]. ITPK1 is a protein modified gene closely related to inositol phosphate metabolism and cell death [39]. Recently, researchers have found that membrane binding and lipid transport induced by inositol phosphate metabolism are important factors in lysosomal driven aging related diseases [40]. In addition, ITPK1 methylation was significantly associated to smoking related CAD [41]. TFAP4 is an important transcription factor involved in DNA repair, thereby inhibiting DNA damage, aging, and chromosomal instability [42]. The detection rate of wild-type homozygous genotype of TCF7L2 gene in middle-aged and elderly CHD patients is significantly higher than that in the control group [43]. Furthermore, TCF7L2 gene polymorphism is associated with reduced insulin secretion, deterioration of endothelial function, increased coronary artery thrombosis burden, and increased short-term mortality in patients with myocardial infarction [44]. Therefore, these ARCGs are important biomarkers for CAD and have the potential to serve as therapeutic targets.

The CIBERSORT results showed that the expression of T cells CD4 naïve was significantly reduced in CAD patients, while the expression of Macrophages M0 was significantly increased. Inflammatory macrophages and foam cell formation are key factors in atherosclerotic plaque progression [45]. M0 macrophages are the initiation point of inflammatory response. Under the stimulation of chemokines, immune complexes and lipids, M0 macrophages can be polarized to pro-inflammatory M1 subsets or anti-inflammatory M2 subsets [46]. In addition, our single-cell analysis results showed that NOX4 was mainly expressed in macrophages. Similarly, Vendrov et al. suggested that increased NOX4 during aging drives mitochondrial dysfunction and a proinflammatory phenotype in macrophages, contributing to atherosclerosis progression [47]. Moreover, Tay et al. reported the importance of interactions between CD4 T cells and B cells to promote lipid-induced atherosclerosis, and that targeting CD4 T cell and B cell interactions may be a therapeutic strategy to limit atherosclerosis progression [48].

Molecular docking can deeply elucidate the interactions between molecules, explain the mechanisms of interactions, and has important applications in drug development [49]. In this study, we explored and preliminarily validated the potential of resveratrol and retinoic acid as CAD treatment drugs through DSigDB and Autodock Vina. Animal study has shown that activating SIRT1 through resveratrol treatment can improve age-related changes in mouse skeletal muscle and heart by restoring autophagy [50]. In addition, Guo et al. found that resveratrol has a significant anti-inflammatory effect, alleviating HIF1A-mediated angiogenesis and preventing the progression of CAD through the TLR4/NF-κB signaling pathway [51]. Moreover, the current use of different carriers (such as nanomaterials) for encapsulation and controlled release of resveratrol has to some extent overcome its limitations of low water solubility and poor chemical stability, thus expanding therapeutic applications [52]. Retinoic acid is a metabolite of vitamin A in the body and plays an important role in myocardial differentiation and maturation [53]. Our study identified that retinoic acid has good binding with FGFR3, HIF1A, and HK3. Bilbija et al. found that retinoic acid signaling is activated in ischemic hearts and can inhibit the differentiation of fibroblasts in vitro, playing a role in the regulation of damage and repair during remodeling [54]. FGFR3 is an independent gene-encoded fibroblast growth factor receptor whose overactivation may lead to coronary endothelial cell dysfunction and vascular wall damage, thereby increasing the occurrence and development of CAD [55].

This study is the first to systematically evaluate aging genes in CAD, identify characteristic genes and biological functions, and predict their potential molecular drugs. However, there are some limitations that need to

be highlighted. Firstly, our current research is on obtaining public databases, despite conducting various bioinformatics mining, its specific mechanisms and reliability require additional clinical or experimental validation and evaluation. In addition, specific aging features such as cellular senescence, vascular senescence, and nutrient-sensing disorders with potential mechanisms of CAD need to be further explored.

Conclusion

In summary, we screened CAD related ARCGs through machine learning, constructed different CAD aging clusters, and explored related functional pathways. Moreover, we explored molecular drugs related to ARCGs and verified their feasibility through molecular docking. These results suggest that aging genes play an important role in the onset and progression of CAD, and molecular drugs that act on their targets have potential therapeutic effects.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-025-02137-0.

Supplementary Material 1

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Author contributions
Conception: Kai Huang, Zijun Chen, Ling Yang and Chun Yang. Interpretation or analysis of data: Kai Huang, Zijun Chen, Ruting Wang and Hangfeng Ying. Preparation of the manuscript: Kai Huang, Zijun Chen, Ruting Wang, Hangfeng Ying, Jiahao Duan, Yi Zhang, Qianyuan Shi, Chun Yang and Ling Yang. Revision for important intellectual content: Chun Yang and Ling Yang. Supervision: Ruting Wang, Hangfeng Ying and Jiahao Duan. All authors reviewed the manuscript.

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Data availability
All the data can be obtained from the open-source website we provide, and the conclusion can be drawn through the analysis of the relevant software. The datasets generated and/or analysed during the current study are available in the Gene Expression Omnibus (GEO) database repository (GSE12288, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE12288;GSE159677, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi).

Declarations

Ethics approval and consent to participate
This study analyzed existing data sets and did not require ethical review.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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