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Identification of Ferroptosis Genes Associated with Osteoarthritis Based on Bioinformatics and Machine Learning

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Abstract: Background: Osteoarthritis (OA) is the most common joint disease, and ferroptosis is a newly discovered form of cell death linked to the pathogenesis of OA, suggesting that ferroptosis-related genes may serve as potential biomarkers. Methods: This study set out to identify differentially expressed ferroptosis-related genes (Ferr-DEGs) associated with OA by looking at the GSE55235 microarray dataset from the GEO database. We employed machine learning algorithms, along with GO and KEGG enrichment analyses, to explore the biological functions and pathways of these genes. Results: We identified a total of 119 Ferr-DEGs, and three ferroptosis-related genes, IDH2, PLIN2, and KLF2, were ultimately determined as diagnostic biomarkers for OA. We confirmed high diagnostic accuracy using ROC curve analysis. Furthermore, an analysis of immune cell infiltration showed strong links between these genes and different types of immune cells, indicating their potential roles in the immune microenvironment of OA. Conclusion: Our findings indicate that IDH2, PLIN2, and KLF2 play a key role in OA development and could serve as promising diagnostic biomarkers. Future studies with larger sample sizes will be needed to validate the roles of these ferroptosis-related genes in OA and their potential as therapeutic targets.

Keywords: Osteoarthritis; Ferroptosis; Biomarkers; Immune Microenvironment; Machine Learning.

1. Introduction

Osteoarthritis (OA) is recognized as the most prevalent joint disease, currently affecting approximately 350 million individuals globally, with a marked increase in incidence noted with advancing age[1]. The molecular mechanisms underlying OA pathogenesis involve various processes, including ferroptosis, oxidative stress, and apoptosis, which contribute to the degeneration of articular cartilage[2, 3]. Specifically, the dysregulation of iron metabolism and the resulting oxidative damage play a crucial role in the disease's progression, highlighting the significance of these pathways in therapeutic targeting[4].

Key signaling pathways implicated in OA include the Forkhead box O (FoxO) signaling pathway and the hypoxia-inducible factor 1 (HIF-1) pathway, both of which regulate critical gene expressions associated with cellular responses to stress and inflammation[5, 6]. Additionally, the regulation of iron death-related genes is increasingly recognized as a relevant aspect of OA pathology, suggesting that these pathways could serve as potential therapeutic targets[7].

Despite advancements in understanding OA's molecular landscape, current diagnostic and therapeutic approaches remain limited. Existing treatments primarily focus on symptomatic relief rather than addressing underlying causes, resulting in a pressing need for the identification of new biomarkers and therapeutic targets[8, 9]. The development of effective disease-modifying agents is crucial for improving patient outcomes and enhancing quality of life for those living with OA, emphasizing the necessity for ongoing research in this area[10].

In summary, the study of ferroptosis-related gene expression in OA presents promising avenues for understanding the disease's mechanisms and developing targeted interventions.

OA is a degenerative joint disease characterized by the progressive deterioration of articular cartilage, leading to pain and functional impairment. The identification of novel biomarkers for OA is crucial for early diagnosis and effective management. In this study, we aim to analyze data from the Gene Expression Omnibus (GEO) database to identify iron death-related genes associated with OA and evaluate their potential as diagnostic biomarkers. We will employ machine learning algorithms in conjunction with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses to explore the role of these genes in the pathogenesis of OA. The integration of these advanced computational methods allows for a comprehensive understanding of the molecular mechanisms underlying OA, potentially leading to the discovery of new therapeutic targets and improving patient outcomes.

2. Method

2.1. Selection of Research Data

The data for this study mainly comes from existing osteoarthritis datasets in the GEO database (https://www.ncbi.nlm.nih.gov/geo/). GSE55235[11] is derived from knee cartilage tissues of 10 normal and 20 OA patients in the GEO dataset microarray chip. Ferroptosis-related genes come from the Ferroptosis Database (FerrDb V2) (http://www.zhounan.org/ferrdb/current/operations/download.html, accessed January 20, 2025)[12], including driver genes, inhibitor genes, and marker genes. We compared the entire set of differentially expressed genes (DEGs) with the genes in FerrDb V2 to identify the common Ferr-DEGs. The

GSE98918[13] dataset was used for external validation.

2.2. Identification of Ferroptosis-Related Differentially Expressed Genes (Ferr DEGs)

The R package "limma" was used to analyze the gene expression differences between OA and normal samples in the GSE55235 dataset (adjusted P value < 0.05). Finally, we crossed the entire set of differentially expressed genes (DEGs) with the ferroptosis gene regulatory factors retrieved from the FerrDb database (http://www.zhounan. org/ferrdb/ current/ operations/ download.html), which includes 264 driver genes, 238 inhibitor genes, and 9 marker genes, to identify the Ferr-DEGs. These are ferroptosis-related genes that may be involved in the pathogenesis of osteoarthritis.

2.3. GO and KEGG Enrichment Analysis

We conducted GO and KEGG enrichment analyses using the R packages "ggplot2," "GOplot," and "cluster-Profiler." GO analysis was conducted at three levels: molecular function (MF), cellular component (CC), and biological process (BP). KEGG is a comprehensive database used to investigate diseases, chemicals, drugs, biological processes, and genomes.

2.4. Selection of OA Ferroptosis Genes

We selected potential OA diagnostic biomarkers from the Ferr-DEGs mentioned earlier by combining two machine learning algorithms: Support Vector Machine Recursive Feature Elimination (SVM-RFE) and Least Absolute Shrinkage and Selection Operator (LASSO) regression. SVM-RFE is a machine learning technique that trains subsets of features from different categories to narrow down the feature set and then selects the most predictive features in a backward manner[14]. LASSO regression was performed using the R package "glmnet" to select valuable variables in the linear model. The response type was set to binomial, and the "one standard error" rule was applied. Finally, we identified the most predictive genes by taking the intersection of the results from SVM-RFE and LASSO regression.

2.5. Diagnostic Value of Osteoarthritis Candidate Genes

We compared the expression levels of candidate genes between the OA group and the control group using Student's t-test, and the diagnostic value of the candidate genes was analyzed using the receiver operating characteristic (ROC) curve from the GSE55235 dataset. Additionally, we selected the GSE98918 dataset for external validation, as it includes 12 OA samples and 12 normal human synovial samples.

2.6. Immune Cell Infiltration Analysis

To evaluate how the immune microenvironment affects OA development, we used the CIBERSORT algorithm[15] (http://cibersortx.stanford.edu) to estimate the abundance of 22 types of infiltrating immune cells in each sample. This algorithm can perform linear support vector regression to deconvolute gene expression profiles. We compared the differences in immune cell infiltration between the OA group and the normal group using the student t-test. Then, the correlation between candidate genes and the abundance of infiltrating immune cells was determined using the Spearman rank correlation test and visualized using the R package "ggplot2."

2.7. Statistical Analysis

All data processing and analysis in this article were based on R software (Version 4.2.2). Unless stated otherwise, we estimated the statistical significance of comparisons between two groups of continuous variables using the independent Student's T-test for normally distributed variables, and the Mann-Whitney U test (Wilcoxon Rank Sum Test) was used to analyze differences between non-normally distributed variables. Results were calculated using Spearman correlation analysis to determine the correlation coefficients between different molecules. If not specifically indicated, all statistical p values were two-tailed, with p value < 0.05 considered statistically significant.

3. Results

3.1. DEGs Related to Ferroptosis in OA

We utilized the GSE55235 microarray dataset (derived from 10 normal and 20 OA human knee cartilage tissue samples in the GEO dataset) to identify Ferr-DEGs. Ferr-DEGs are defined as the intersection of all DEGs (adjusted P value < 0.05) with the list of ferroptosis-related genes defined by FerrDb[12]. A total of 119 Ferr-DEGs were identified in the OA group compared to the normal control group (**Figure 1**A).

A: heatmap of Ferr DEG; B: expression in each sample the top 10 enriched pathways of Ferr DEG in GO; C: expression in each sample Enrichment pathway of Ferr DEG in KEGG

3.2. GO Analysis and KEGG Pathway Analysis

To explore the biological activities and pathways associated with Ferr-DEGs in OA cases, GO and KEGG enrichment analyses were performed. The top 10 enriched pathways for GO and KEGG terms are shown in **Figure 1** B-C. The analysis was divided into three levels: Molecular Function (MF), Cellular Component (CC), and Biological Process (BP). In BP, ferroptosis-related DEGs were enriched in responses to: response to nutrient levels,response to oxidative stress,cellular response to chemical stress,cellular response to external stimulus,response to oxygen levels,response to starvation,response to hypoxia,response to decreased oxygen levels,cellular response to oxidative stress and cellular response to extracellular stimulus. In terms of CC, they were mainly enriched in autophagosome,apical part of cell,peroxisome,microbody,NADPH oxidase complex,apical plasma membrane,autophagosome membrane,peroxisomal membrane,microbody membrane and melanosome. For MF, these genes were enriched in ubiquitin protein ligase binding, ubiquitin-like protein ligase binding, RNA polymerase II-specific DNA-binding transcription factor binding, superoxide-generating NAD(P)H oxidase activity, DNA-binding transcription factor binding, oxidoreductase activity acting on NAD(P)H, oxidoreductase activity acting on NAD(P)H with oxygen as acceptor, protein serine/threonine kinase activity, flavin adenine dinucleotide binding, and protease binding. Additionally, the KEGG pathway analysis results for ferroptosis-related DEGs are shown in **Figure 1**C. They were mainly enriched in Ferroptosis, FoxO signaling pathway, Autophagy - animal, AGE-RAGE signaling pathway in diabetic complications, Human T-cell leukemia virus 1 infection, HIF-1 signaling pathway, NOD-like receptor signaling pathway, Hepatitis B, Lipid and

atherosclerosis, Prostate cancer, and Human cytomegalovirus infection, among others.

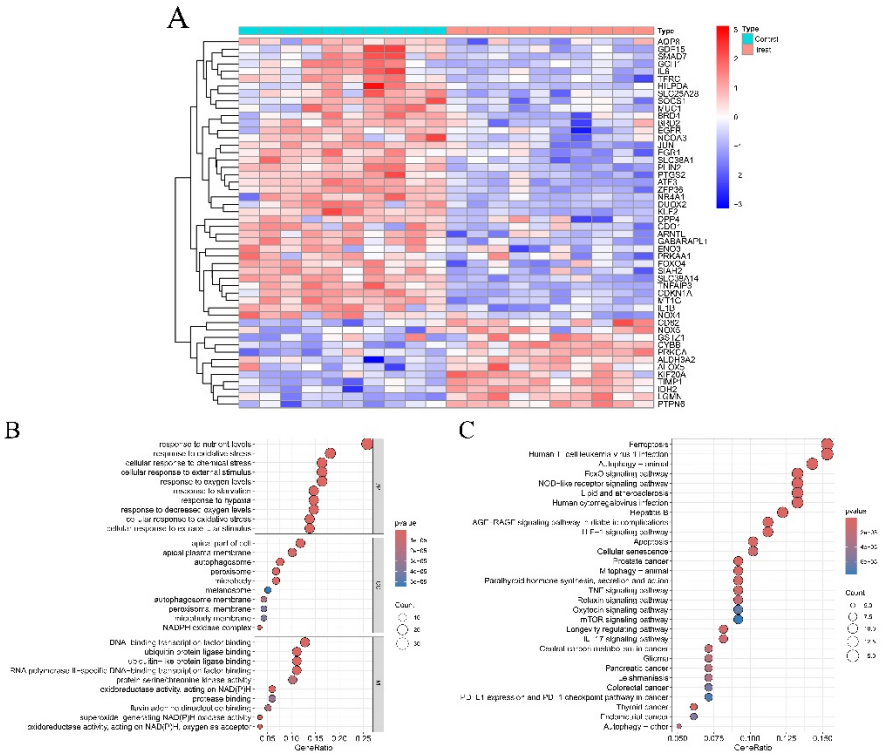

Figure 1. Ferr DEG and its functional enrichment

3.3. Selection of Ferroptosis-Related Diagnostic Genes for OA

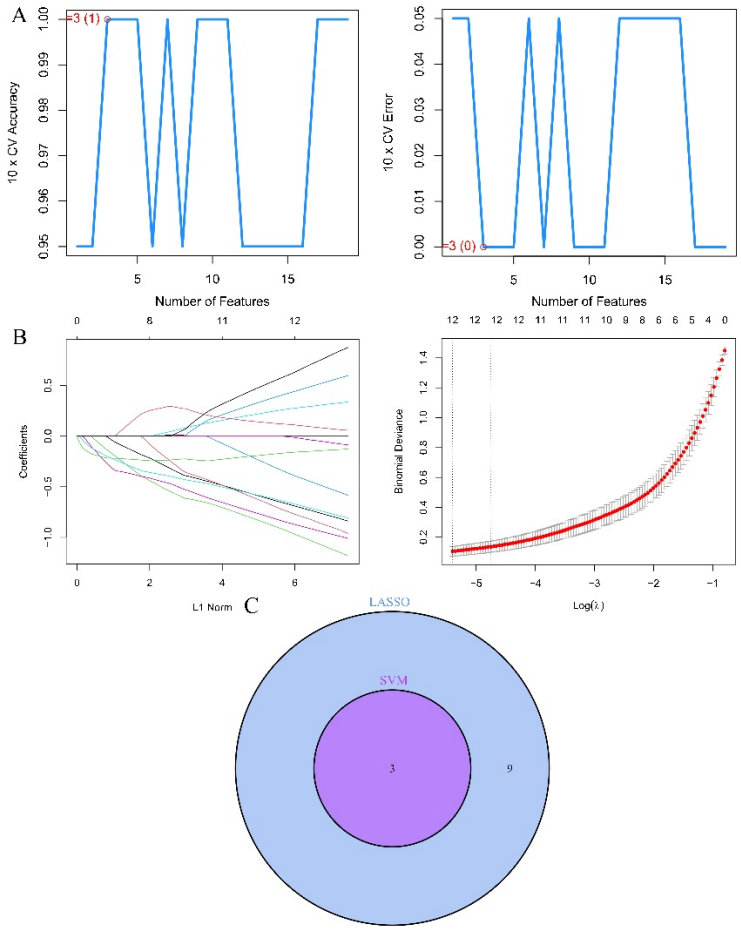

Figure 2. Select candidate genes for OA diagnosis from Ferr DEG

A: Validate candidate gene expression through SVM-RFE selection. B: Adjustment of feature selection in LASSO regression model. C: The Venn diagram displays three common genes shared by the SVM-RFE and LASSO methods

To identify more reliable candidate genes, we employed two machine learning algorithms to determine OA diagnostic biomarkers from Ferr-DEGs. SVM-RFE selected the three most predictive features (Figure 2A), while LASSO regression selected nine predictive genes from statistically significant univariate analyses (Figure 2B). We used a Venn diagram to show the intersection of the two methods, ultimately identifying three OA ferroptosis-related diagnostic genes: Isocitrate Dehydrogenase (NADP (+)) 2 (IDH2), Adipose differentiation-related protein (PLIN2), and KLF Transcription Factor 2 (KLF2) as potential OA diagnostic biomarkers (**Figure 2**C).

3.4. Diagnostic Value of Ferroptosis-Related Genes for Osteoarthritis

To validate the diagnostic value of these three ferroptosis-related diagnostic genes IDH2, PLIN2, and KLF2 for OA, we assessed their performance in the training set GSE55235, where they all showed excellent diagnostic accuracy (**Figure 3**A-B). In the external validation set GSE98918, they also demonstrated good diagnostic accuracy: IDH2 (AUC: 0.799, 95% CI: 0.590-0.958), PLIN2 (AUC: 0.722, 95% CI: 0.500-0.903), KLF2 (AUC: 0.917, 95% CI: 0.785-1.000) (**Figure 3**C-E).

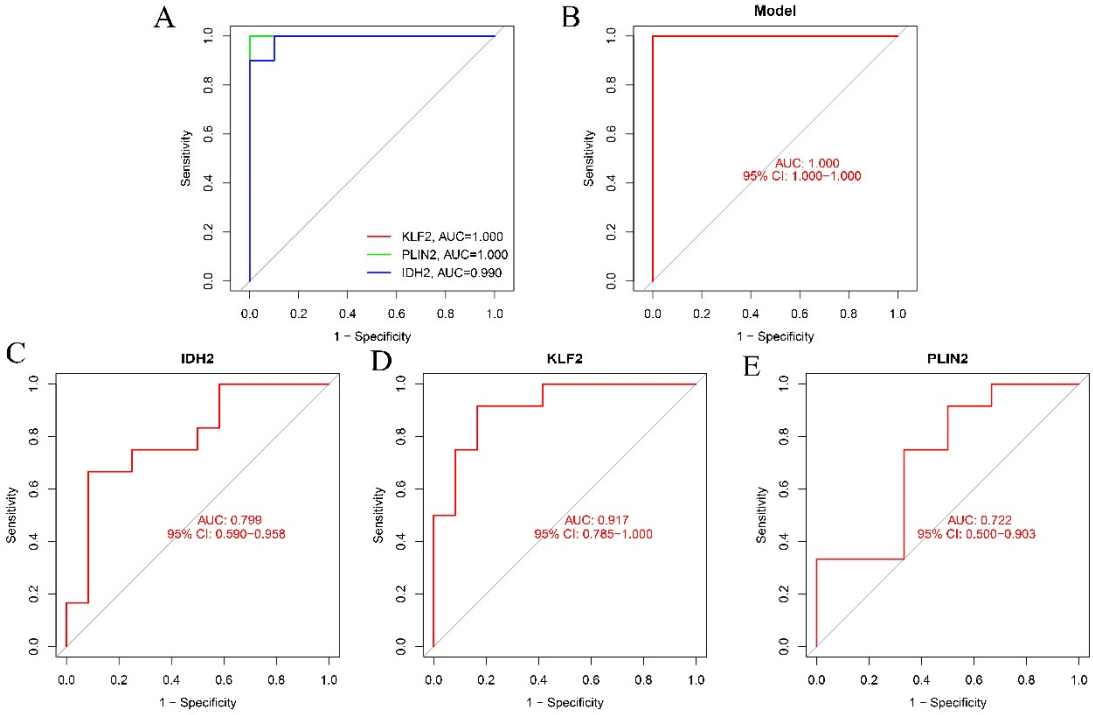

Figure 3. The diagnostic value of candidate genes in the training set GSE55235 and validation set GSE98918

A-B: ROC curve for OA diagnosis in GSE55235; C-E: ROC curve for OA diagnosis in GSE98918

3.5. Association of Immune Cell Infiltration with OA Ferroptosis-Related Diagnostic Genes

The inflammatory and immune microenvironment plays a crucial role in the pathogenesis of OA. CIBERSORT-based immune cell infiltration analysis is a valuable tool for understanding the disease process[15]. We used CIBERSORT to generate immune cell infiltration in OA and normal control samples from the GSE55235 dataset, showing the relative proportions of 22 immune cell types (**Figure 4**A). Compared to the normal control group, the OA group had higher levels of Plasma cells and resting Mast cells. In contrast, the infiltration of CD4 memory T cells, M1 Macrophages, and activated Mast cells was lower in the OA group. Next, we analyzed the association of IDH2, PLIN2, and KLF2 with immune cell infiltration in OA (**Figure 4**B). Several immune cell infiltrations were found to be significantly correlated with the expression of IDH2, PLIN2, and KLF2. Specifically, PLIN2 was negatively correlated with memory B cells and resting NK cells ($P < 0.05$), KLF2 was positively correlated with follicular helper T cells ($P < 0.05$), and IDH2 was positively correlated with M2 Macrophages and follicular helper T cells ($P < 0.05$) while negatively correlated with resting CD4 memory T cells ($P < 0.05$). This suggests that IDH2, PLIN2, and KLF2 might be important in these immune cells, potentially affecting the development of OA. These findings provide valuable evidence for future research.

A: Comparison of immune cell infiltration between OA and normal control;B: The correlation between IDH2, KLF2, and PLIN2 and infiltrating immune cells in OA

4. Discussion

OA is a prevalent degenerative joint disease characterized by the progressive deterioration of articular cartilage, leading to pain and functional impairment. Current treatment strategies primarily focus on symptom management rather than addressing the underlying pathophysiological mechanisms, highlighting the urgent need for novel diagnostic and therapeutic approaches. Our study identifies the critical roles of iron death-related genes, specifically Isocitrate Dehydrogenase (NADP (+)) 2 (IDH2), Adipose

Differentiation-Related Protein (PLIN2), and KLF Transcription Factor 2 (KLF2), in the pathogenesis of OA, underscoring their potential as diagnostic biomarkers.

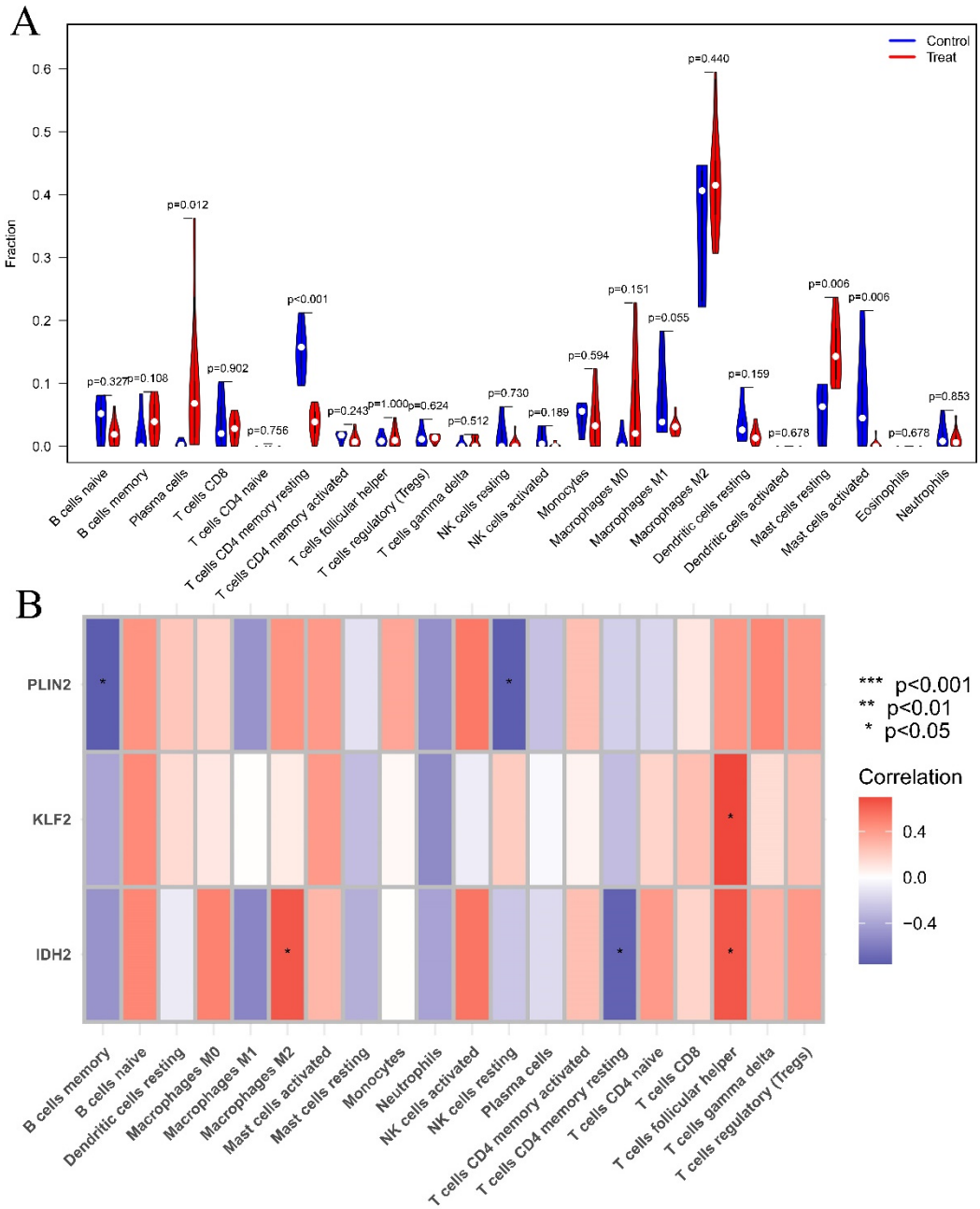

Figure 4. Immune cell infiltration in OA

By integrating phenotypic data with advanced machine learning techniques, we successfully identified these three genes as significant predictors of OA. The application of Support Vector Machine-Recursive Feature Elimination (SVM-RFE) and LASSO regression allowed us to refine our candidate gene list, enhancing the reliability of our findings. The diagnostic accuracy of IDH2, PLIN2, and KLF2 was validated in both training and external validation datasets, demonstrating their potential utility in clinical settings. This research not only elucidates the molecular mechanisms underlying OA but also paves the way for future studies aimed at improving disease diagnosis and management.

The study identified three iron death-related genes, IDH2, PLIN2, and KLF2, which exhibited significant expression differences in OA patients, suggesting their potential as diagnostic biomarkers for the disease. IDH2, known for its role in the tricarboxylic acid cycle, is crucial for cellular metabolism and energy production[16]. Its dysregulation has been implicated in various diseases, including cancer and neurodegenerative disorders, highlighting its importance in maintaining cellular homeostasis[16, 17]. In the context of OA, the elevated expression of IDH2 may indicate its involvement in the metabolic alterations associated with the disease, potentially serving as a marker for disease severity and progression. PLIN2, a lipid droplet protein, plays a vital role in lipid metabolism and storage[18, 19], and its upregulation in OA patients suggests a link between altered lipid metabolism and the inflammatory processes characteristic of OA. The findings indicate that PLIN2 may contribute to the pathophysiology of OA by modulating inflammation and cellular stress responses, thus representing a promising target for therapeutic intervention. KLF2, a transcription factor known for its anti-inflammatory properties, has been shown to regulate various cellular processes, including endothelial function and immune responses[20]. Studies had shown that KLF2 may alleviate

pulmonary fibrosis and inflammation by regulating AP-1[21]. The significant expression differences of these genes in OA patients not only provide insights into the underlying mechanisms of the disease but also highlight their potential utility as biomarkers for early diagnosis and targeted therapies in OA management. Further research is warranted to elucidate the precise roles of IDH2, PLIN2, and KLF2 in OA and to explore their applicability in clinical settings.

The results of the GO and KEGG analyses indicate that ferroptosis-related differentially expressed genes (DEGs) are significantly enriched in several critical biological processes and signaling pathways associated with OA. Specifically, the enrichment of these genes in pathways such as the FoxO signaling pathway, which is known to regulate oxidative stress responses, suggests a potential mechanism by which ferroptosis may influence chondrocyte survival and function in the context of OA. Additionally, pathways related to autophagy and the response to oxidative stress highlight the interplay between cellular stress responses and the pathogenesis of OA. The identification of these pathways underscores the importance of ferroptosis in the disease process, as it may contribute to the degradation of the extracellular matrix and the overall deterioration of joint health. This research provides valuable insights into the molecular mechanisms underlying OA, suggesting that targeting ferroptosis and its associated pathways could represent a novel therapeutic strategy for managing this prevalent joint disorder. By elucidating the role of ferroptosis in OA, this study not only enhances our understanding of the disease but also opens avenues for the development of targeted interventions aimed at mitigating cartilage degeneration and improving patient outcomes. The findings align with recent literature that emphasizes the significance of ferroptosis in various degenerative diseases, reinforcing the notion that modulating this form of cell death may have therapeutic implications in OA management [22, 23].

The immune microenvironment plays a crucial role in the pathogenesis of OA, characterized by the infiltration of various immune cells that contribute to inflammation and tissue degeneration. Our immune cell infiltration analysis revealed significant associations between the expression of iron death-related genes, specifically IDH2, PLIN2, and KLF2, and the presence of different immune cell types within the OA synovium. Notably, the expression of IDH2 was positively correlated with M2 macrophages and follicular helper T cells, suggesting a potential role in promoting an anti-inflammatory environment, while PLIN2 showed a negative correlation with memory B cells and natural killer cells, indicating its involvement in modulating immune responses. These findings underscore the importance of these genes in shaping the immune landscape of OA, highlighting their potential as biomarkers for disease progression and therapeutic targets. The identification of these relationships not only enhances our understanding of the immune mechanisms underlying OA but also suggests that targeting these pathways may provide novel strategies for managing the disease. By elucidating the interactions between iron death-related genes and immune cell infiltration, this study contributes valuable insights into the complex interplay of metabolic and immune factors in OA, paving the way for future research aimed at developing more effective treatments for this debilitating condition.

This study has several limitations that must be acknowledged. The relatively small sample size may restrict the generalizability of our findings, and larger-scale clinical validation is essential to confirm the role of ferroptosis-related genes in osteoarthritis (OA) and their potential as biomarkers. Additionally, the absence of wet lab experiments to validate the in silico findings raises concerns about the robustness of the identified diagnostic genes. Furthermore, the use of a single dataset may introduce batch effects, which could affect the reproducibility of the results across different populations.

In summary, our analysis identified three potential diagnostic biomarkers for OA— IDH2, PLIN2, and KLF2. Future research should focus on larger cohorts and functional studies to elucidate the biological mechanisms underlying these associations and to explore their clinical applicability in OA management.

Acknowledgments

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