Original paper

Identification of metabolism regulators as diagnostic markers for ulcerative colitis and their correlation with immune infiltration

Qilong Duan[1], Peng Liu[1], Hualei Chen[2], Yuanyuan Ding[2], Xiaoming Xu[2]

[1]Shandong Medical College, Jinan, China
[2]Department of Gastroenterology, Jining No. 1 People's Hospital, Jining, China

This study determined novel metabolism-related diagnostic biomarkers for ulcerative colitis (UC) and assessed their correlation with immune cell infiltration levels. Transcriptome data of UC was downloaded from the Gene Expression Omnibus (GEO) database, metabolism-related genes were summarised from the Gene Set Enrichment Analysis (GSEA) database. A total of 537 metabolism-related differentially expressed genes (DEGs) in UC were applied to functional enrichment analysis. We processed least absolute shrinkage and selection operator (LASSO) regression analysis and support vector machine-recursive feature elimination (SVM-RFE). We obtained 6 potential metabolism-related diagnostic biomarkers (CHST13, ETNK1, LPCAT1, PDE6A, PLA2G2A, and UGT2A3). Expression patterns and diagnostic ROC curves were depicted in both the training and testing cohorts to verify their diagnostic value. Immune infiltration analysis indicated that UC samples have more abundant infiltration levels of immune cells. Furthermore, the upregulated diagnostic biomarkers significantly positively correlated with B cell memory, T cell CD4 memory activated, dendritic cells activated, etc., while the downregulated ones mainly significantly positively correlated with mast cells resting, NK cells activated, and macrophages M2. Our study primarily identified 6 metabolism regulators (CHST13, ETNK1, LPCAT1, PDE6A, PLA2G2A, and UGT2A3) as potential diagnostic biomarkers for UC and determined their correlation with immune infiltration.

Key words: ulcerative colitis, gene expression omnibus, machine learning, diagnostic markers, bioinformatics, immune infiltration.

Introduction

Ulcerative colitis (UC) is a common subtype of inflammatory bowel disease (IBD), characterised by chronic course and high relapse rate [1, 2]. As the name suggests, improper immune response is deemed to be the main aetiology of UC, which may comprehensively result from microbiome dysbiosis, dysregulation of local immune microenvironment, genetic alteration, and socio-psychological factors [3, 4]. Restraint in mucosa and submucosa with performance of diffuse shallow ulcers is the main pathological characteristic of UC; invasion to external layers of intestine wall is not common [5, 6]. Because of the high relapse rate and exhaustible course, patients with UC suffer from great disease burden. Thus, it is urgent to further explore the molecular

mechanisms of UC and exploit dependent and valuable biomarkers and targets for early diagnosis and better outcome improvement for patients with UC.

Cellular metabolism disorder has been proven to be an essential composition or initiation for various human diseases [7]. Likewise, cellular metabolism disorder also attaches great importance to the pathogenesis of UC. Regional microbiota and gut immune microenvironment may result in metabolism disorder, so as to induce, propel, and interact with UC [8, 9]. TLR4/NF-κB has been the key signalling transduction pathway in inflammatory response [10]. Low-dose sucrose intake per day could alleviate ulcerative colitis in mice with increased short chain fatty acids production by restoring gut microbiota. Consistently, MAPK/NF-κB cascade inhibition by elevated PPAR-γ was observed [11]. Ferroptosis results from dysregulation of iron metabolism, which was observed in UC pathogenesis and assessed as potential therapeutic targets [12]. In addition, oxidative stress-associated metabolic alterations also played a role in UC [13, 14]. It is becoming apparent that metabolism exerts a great influence on UC initiation and development. Previous studies have revealed several metabolism regulators as emerging diagnostic biomarkers or drug targets in UC [15–17]. However, relevant work has not been fully elucidated yet. Thus, it is necessary to further explore the potential value of metabolism regulators as candidate diagnostic biomarkers for UC. In this present study, we tried to identify metabolism regulators that are different from the reported ones, as potential diagnostic biomarkers in UC, and primarily assess their correlations with immune infiltrating cells. Initially, the transcriptome data of UC from the Gene Expression Omnibus (GEO) database were downloaded whereby to determine differentially expressed genes (DEGs) between UC samples and normal samples. Then LASSO regression analysis and SVM-RFE were applied to further screen potential diagnostic biomarkers for UC. The expression pattern and diagnostic ROC curve for each diagnostic biomarker were verified. Subsequently, CIBERSORT was utilised to assess the difference of immune cells infiltration between UC and the normal. Distinctive immune correlation patterns were further identified between diagnostic biomarkers and infiltration levels of 22 immune cells, rendering new insights into the immune-related pathogenesis of UC at a cellular level.

Material and methods

Data acquisition

Transcriptome data of GSE92415 and GSE179285 were downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo); the former was selected as a training cohort while the latter was selected as the test cohort. Diverse metabolism-associated signalling pathways and their constitutive regulators were obtained from the Gene Set Enrichment Analysis database (http://www.gsea-msigdb.org).

Determination of metabolism-associated differentially expressed genes and functional enrichment analysis

R software was used to analyse the obtained profiles. The "ggplot2" package was used to process principal component analysis (PCA) to determine the normalisation between UC samples and normal samples. The "limma" package was applied to screen DEGs between UC samples and normal samples. Then we determined metabolism-associated DEGs in UC; metabolism-associated genes with $p < 0.05$ and $|\log_2 \text{FC}| > 0.5$ (FC, fold change) were considered as metabolism-associated DEGs. A volcano plot was drawn using the "DESeq2" package. Then we processed functional enrichment analysis of the identified metabolism-associated DEGs using the "clusterProfiler" package – categories included Gene Ontology (GO: biological process, cellular component and molecular function), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Gene Set Enrichment Analysis (GSEA). C2.all.v6.2.symbols.gmt was selected as the reference gene set. False discovery rate < 0.05 and $p < 0.05$ were set as the cutoff criteria.

Identification of diagnostic biomarkers

Least absolute shrinkage and selection operator (LASSO) regression and support vector machine recursive feature elimination (SVM-RFE) were carried out to filter candidate genes from metabolism-associated DEGs for UC. LASSO regression analysis and SVM-RFE were operated by the "glmnet" package and the "e1071" package, respectively. After both of these, we intersected the results of LASSO regression analysis and SVM-RFE. Genes from the overlap were deemed as diagnostic biomarkers for UC, which were also named as hub genes. The expression pattern of hub genes between UC samples and normal samples were visualised in both the training cohort and the test cohort with the "ggplot2" package. Diagnostic ROC curve of each corresponding hub gene was analysed and depicted in both the training cohort and the test cohort with the "pROC" package and the "ggplot2" package.

Assessment of infiltration level of immune cells

We uploaded the transcriptome matrix profile of the training cohort to CIBERSORT (https://ciber-

sort.stanford.edu) and obtained the corresponding immune cell infiltration matrix data. The difference of infiltration level of immune cells between UC samples and normal samples were illustrated by means of heatmap and boxplot with the "ggplot2" package. Furthermore, the correlation between immune cells in UC were visualised using the "corrplot" package.

Correlation between diagnostic biomarkers and immune cells

The "ggstatsplot" package was used to perform Spearman correlation analysis between expression of diagnostic biomarkers and infiltration level of immune cells, the result of which was visualised using the "ggplot2" package.

Statistical analysis

Statistical analysis was all conducted using the R software. The expressive correlation was identified by Pearson's R and statistical significance. An absolute value of R more than 0.1 was considered to be relevant, and $p < 0.05$ was deemed as statistically significant. "*" indicates $p < 0.05$, "**" indicates $p < 0.01$, "***" indicates $p < 0.001$, and "****" indicates $p < 0.0001$ throughout this study.

Results

Raw data

GSE92415 was selected as training cohort containing 53 UC samples and 21 normal samples, while GSE179285 was selected as a test cohort containing 55 UC samples and 31 normal samples. A total of 186 metabolism-associated signalling pathways were collected from the GSEA website, and 860 metabolism-associated genes were determined for further analysis.

DEG screening and functional characterisation

Two-dimensional PCA showed the normalisation of UC samples and normal samples in the training cohort based on transcriptome matrix, which indicated that the sample source is reliable (Fig. 1A). Then DEGs were assessed via differential expression analysis, the result of which was displayed as a volcano plot (Fig. 1B), among which 537 DEGs were metabolism-associated. A total of 537 metabolism-associated genes were differentially expressed and identified in UC compared to the normal. After that, GO/KEGG functional enrichment analysis revealed that these differentially expressed metabolism regulators

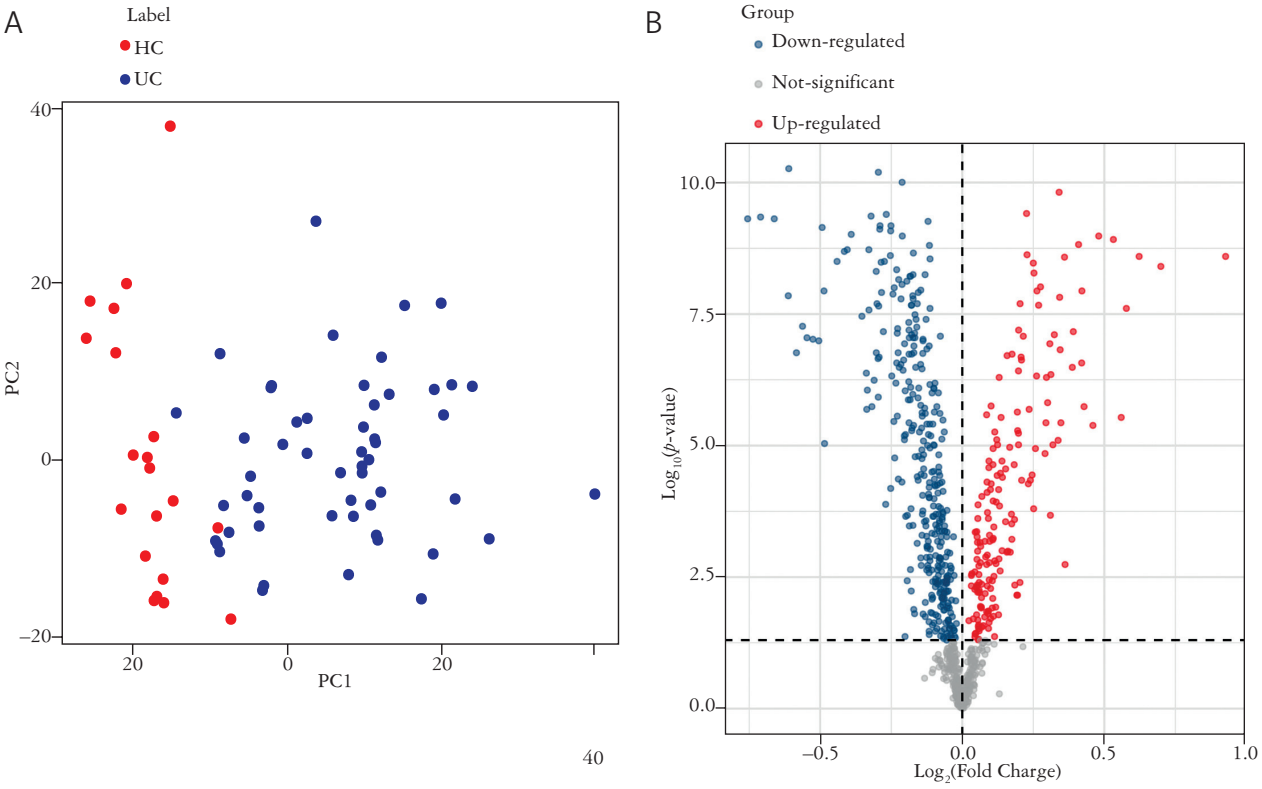

Fig. 1. PCA and differential expression analysis: **A)** Two-dimensional PCA to show the normalisation of UC samples and normal samples. **B)** Volcano plot to display the DEGs

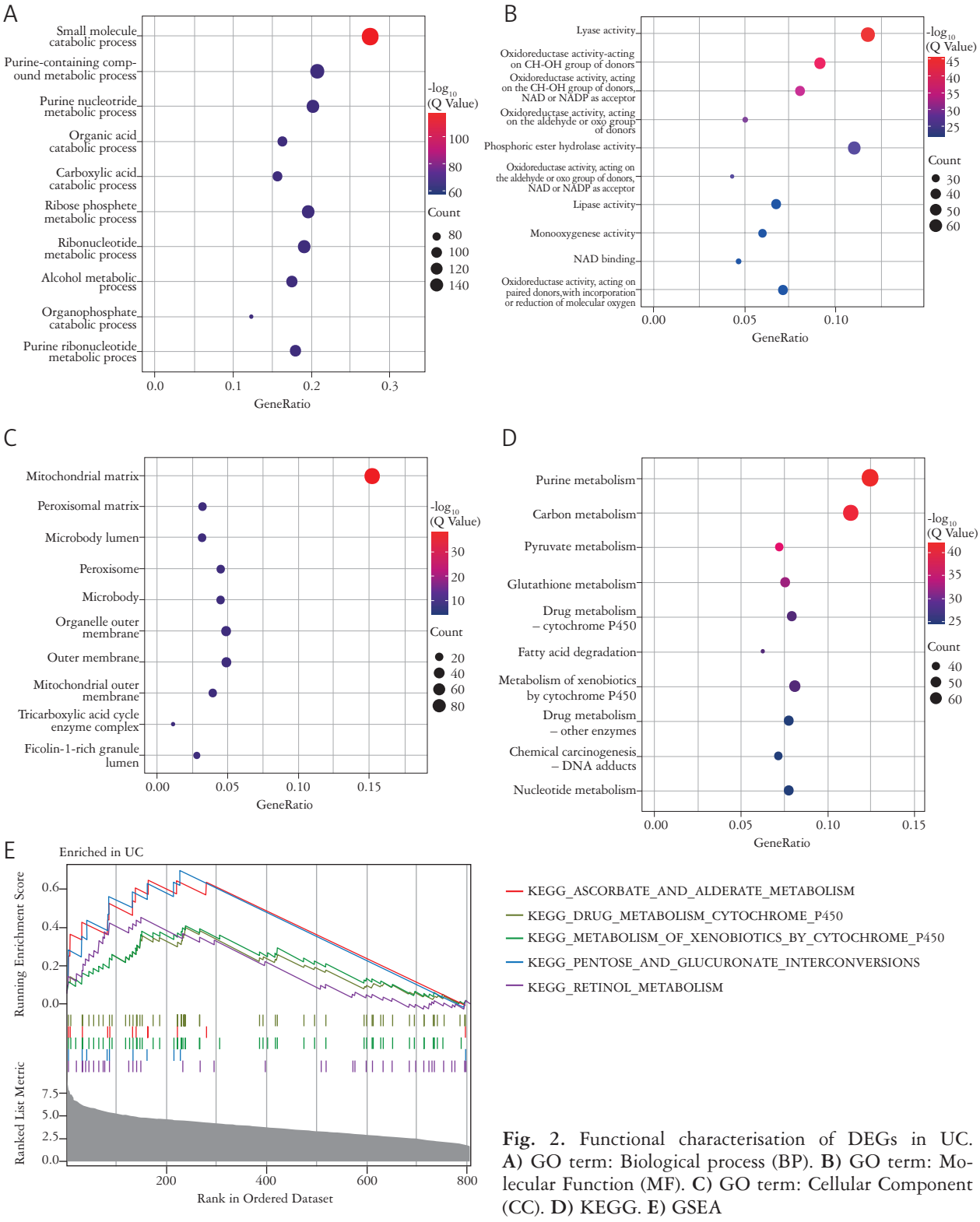

Fig. 2. Functional characterisation of DEGs in UC. **A)** GO term: Biological process (BP). **B)** GO term: Molecular Function (MF). **C)** GO term: Cellular Component (CC). **D)** KEGG. **E)** GSEA

are significantly associated with small molecule catabolic process, mitochondrial matrix, lyase activity, and purine metabolism *et al*. (Fig. 2A–D). The most enriched functional pathway of these differentially expressed metabolism regulators determined by GSEA was pentose and glucuronate interconversions, while others included ascorbate and aldarate metabolism and retinol metabolism *et al*. (Fig. 2E).

Hub genes determination and diagnostic value

LASSO regression analysis and SVM-RFE were applied to filter potential diagnostic biomarkers from

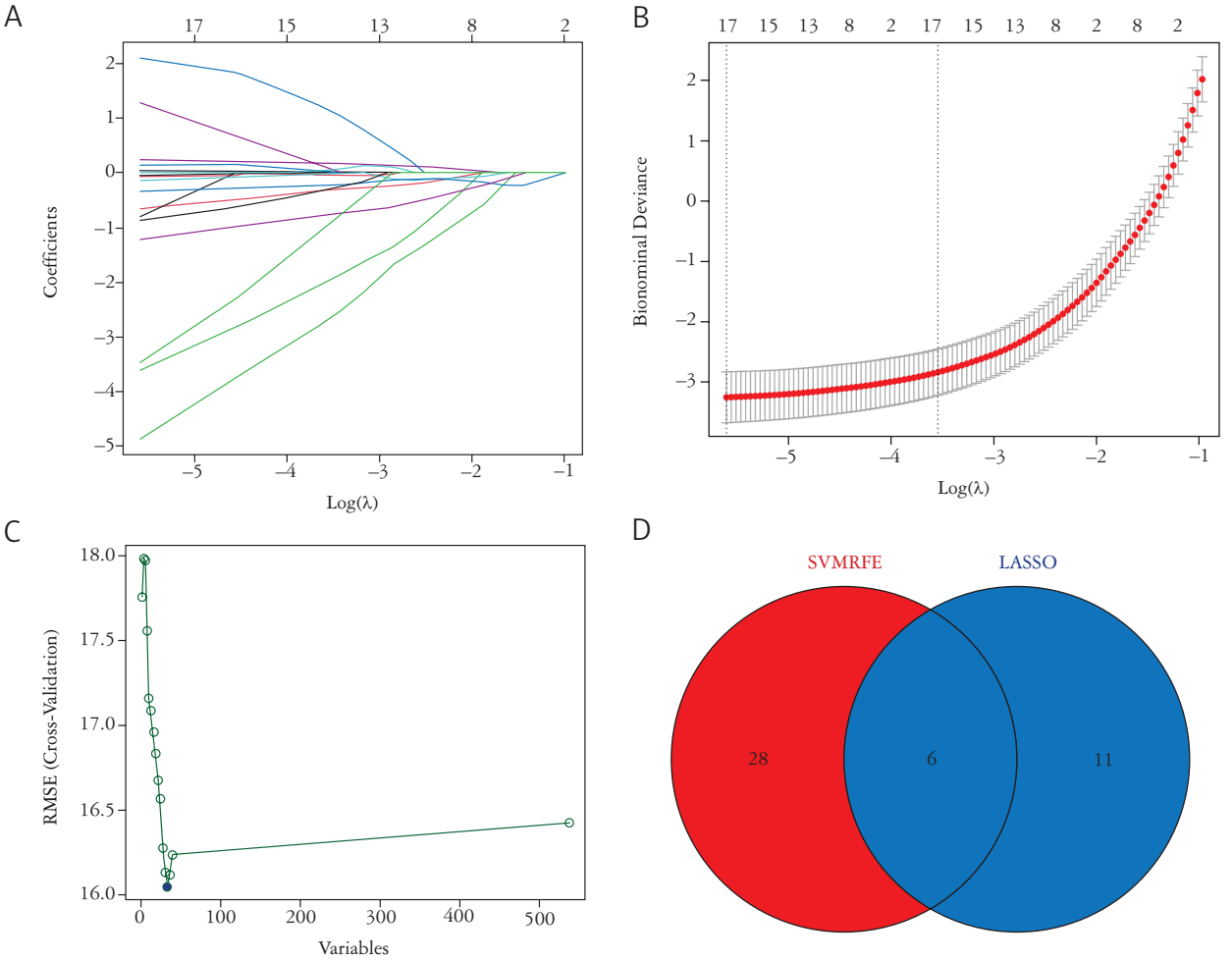

Fig. 3. Determination of hub genes. **A, B)** LASSO regression analysis to filter potential diagnostic biomarkers. Different colours represent different genes. **C)** SVM-RFE to filter potential diagnostic biomarkers. **D)** Venn gram showing the overlap of the 2 algorithms

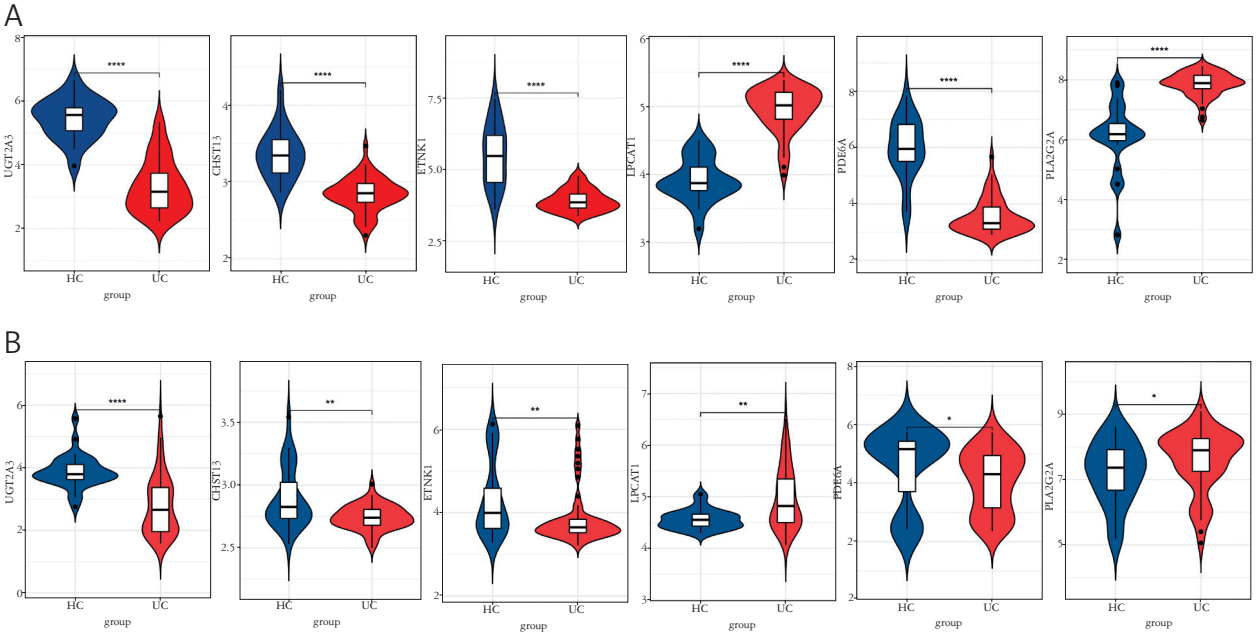

Fig. 4. Expression pattern of hub genes. **A)** Expression pattern of the 6 diagnostic biomarkers in the training cohort. **B)** Expression pattern of the 6 diagnostic biomarkers in the test cohort

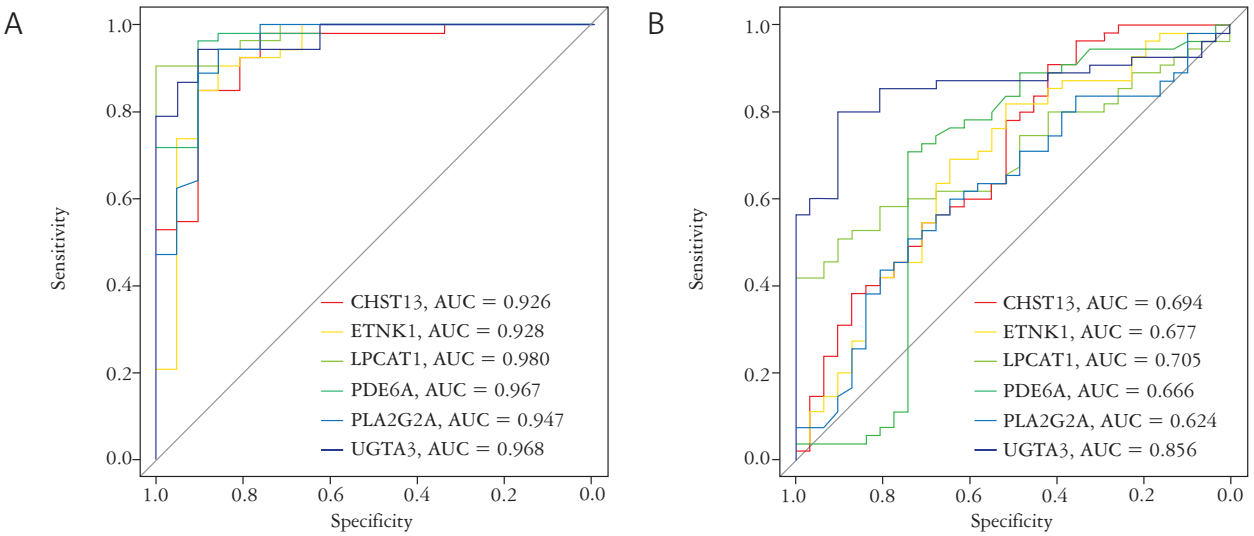

Fig. 5. Diagnostic value of hub genes. **A)** ROC curve of each diagnostic biomarker in training cohort. **B)** ROC curve of each diagnostic biomarker in test cohort

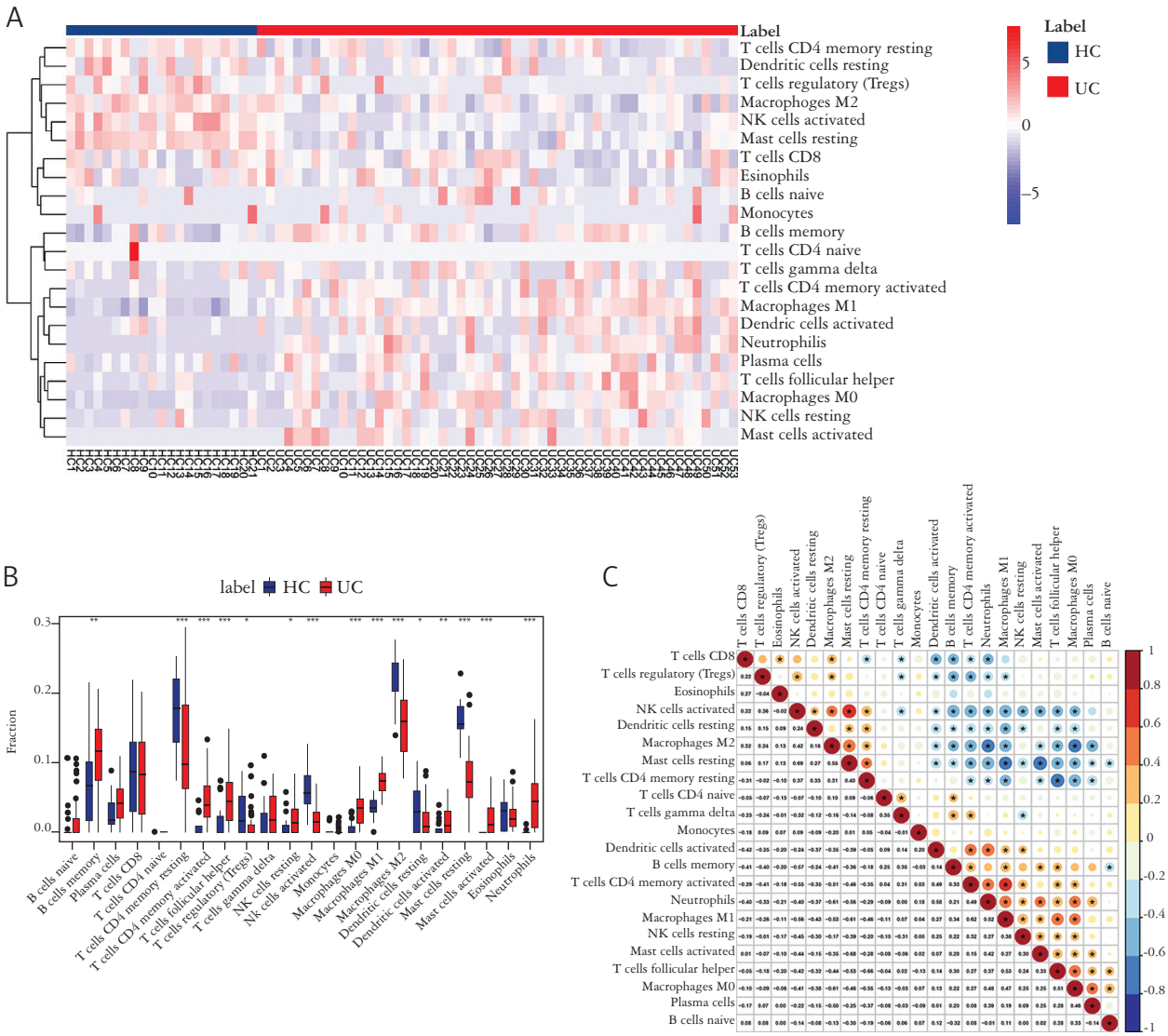

Fig. 6. Assessment of immune cell infiltration in UC. A) Heatmap displaying the infiltration levels of immune cells in the training cohort. **B)** Boxplot displaying the infiltration levels of immune cells in th etraining cohort. **C)** Correlation among 22 immune cells in UC

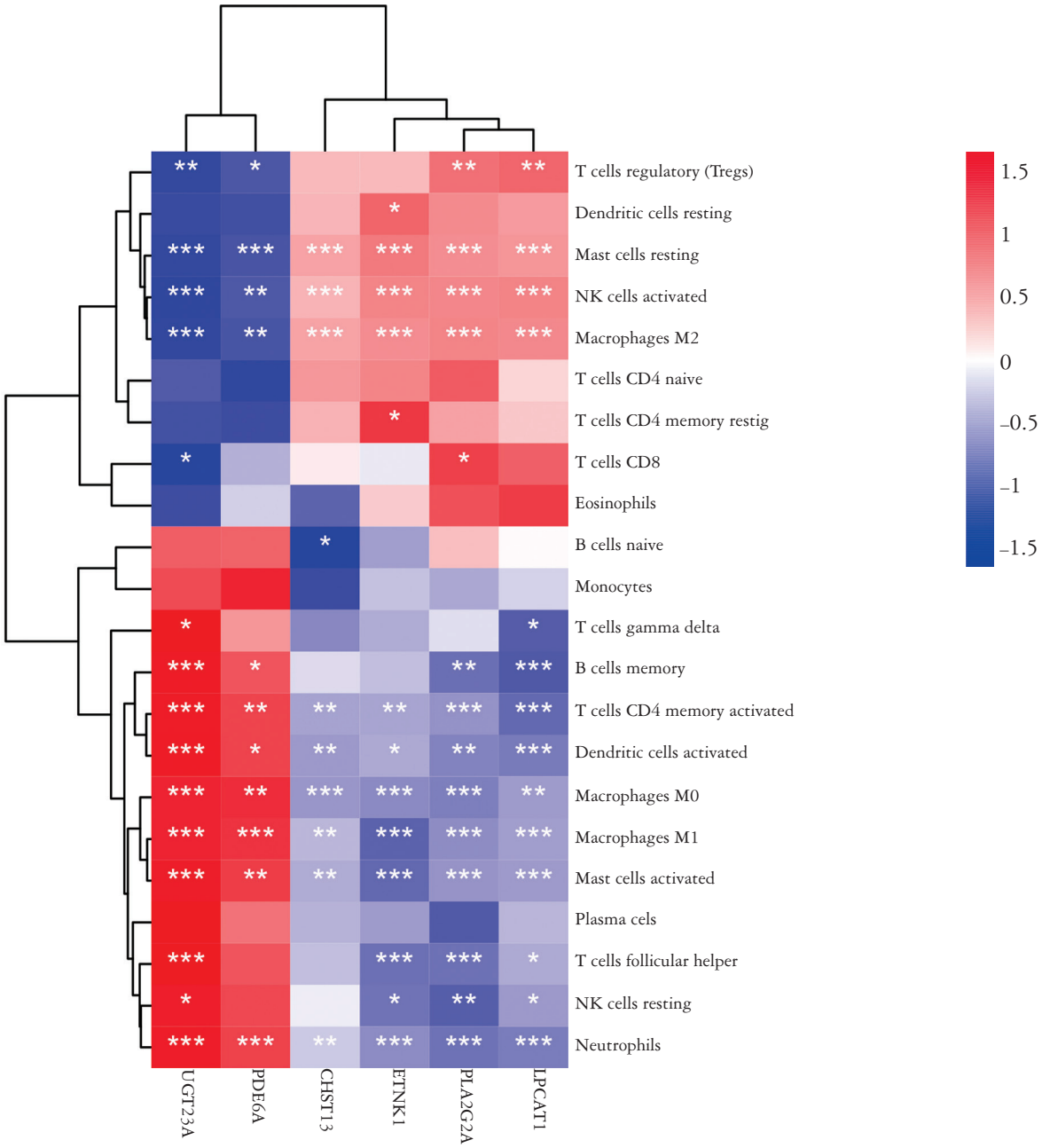

Fig. 7. Correlation between 6 diagnostic biomarkers and 22 immune cells

the differentially expressed metabolism regulators, respectively. As a result, LASSO regression analysis determined 17 potential diagnostic biomarkers, while SVM-RFE determined 34 potential diagnostic biomarkers (Fig. 3A–C). We then intersected the respective candidate genes, revealing 6 hub genes: *CHST13*, *ETNK1*, *LPCAT1*, *PDE6A*, *PLA2G2A*, and *UGT2A3* (Fig. 3D). The expression pattern of the 6 diagnostic biomarkers were illustrated in both the training cohort and the test cohort (Fig. 4A, B). All 6 hub genes showed significantly differential expression between UC and the normal; in particular, LPCAT1 and PLA2G2A were upregulated in UC, while the other 4 were downregulated in UC. Moreover, the diagnostic ROC curve of each of the hub genes was depicted to verify their diagnostic capability in both cohorts (Fig. 5A, B). The area under the curve (AUC) was calculated for each hub gene, rang-

ing from 0.624 (PLA2G2A) to 0.856 (UGT2A3), revealing a certain degree of accuracy for diagnosis.

Immune cells infiltration in ulcerative colitis

The infiltration levels of diverse immune cells in UC were demonstrated by means of heatmap and boxplot (Fig. 6A, B). The results revealed that there are significantly more abundant infiltration levels of B cells memory, T cells CD4 memory activated, T cells follicular helper, NK cells resting, macrophages M0, macrophages M1, dendritic cells activated, mast cells activated, and neutrophils in UC, compared to the normal. On the contrary, the infiltration levels of T cells CD4 memory resting, T cells regulatory (Tregs), NK cells activated, macrophages M2, dendritic cells resting, and mast cells resting were significantly lower in UC. The correlation between 22 types of immune cells are displayed in Fig. 6C. Mast cells resting significantly positively correlated with NK cells activated with the highest correlation index, which was 0.69. Mast cells activated significantly negatively correlated with mast cells resting, with a correlation index of –0.68.

Correlation between 6 diagnostic biomarkers and 22 immune cells

As displayed in Fig. 7, LPCAT1 and PLA2G2A, the 2 upregulated diagnostic biomarkers in UC, showed distinctive immune correlation in contrast to the other 4 downregulated diagnostic biomarkers in UC. The upregulated diagnostic biomarkers mainly significantly positively correlated with B cells memory, T cells CD4 memory activated, and dendritic cells activated *et al*., while the downregulated ones mainly significantly positively correlated with mast cells resting, NK cells activated, and macrophages M2. Immune cells including T cells CD4 naive, T cells CD4 memory resting, T cells CD8, eosinophils, B cells naive, monocytes, and γδ T cells nearly remained silent in correlation with the 6 diagnostic biomarkers.

Discussion

Ulcerative colitis is characterised by a long course and high relapse rate, rendering difficulties for clinical therapy at late point [3, 18]. To date, the most convincing method to diagnose UC remains intestinal endoscopy. However, on account of nonspecific clinical manifestation and lack of reliable serum biomarkers, many patients have entered medium-late course before the endoscopic diagnosis comes. Cellular metabolism disorder has been explored to influence the pathogenesis of many diseases [19, 20]. Metabolism-associated genes or metabolism regulators are widely chosen and identified as potential biomarkers and targets for diagnosis and therapy [21, 22]. Hence, it is important to exploit novel biomarkers, especially metabolism-associated genes, for early diagnosis of UC. Our study screened 6 potential diagnostic biomarkers for UC and analysed their correlation with immune cells. Furthermore, the infiltration pattern of immune cells in UC was elucidated. A total of 537 metabolism-associated genes were shown to be differentially expressed in UC. Primary functional characterisation was carried out for the 537 metabolism-associated genes. GO/KEGG functional enrichment analysis revealed that they are significantly associated with small molecule catabolic process, mitochondrial matrix, lyase activity, and purine metabolism *et al.* Azathioprine, a kind of purine analogue, has been applied as an essential drug for UC treatment for a long time [23]. Purine metabolism was shown to be the most enriched pathway from our KEGG functional enrichment analysis, indicating the accuracy of our analysis. Besides, mitochondria dysfunction is reported to be involved in UC development [24], which is also consistent with one of our GO functional enrichment results showing that the mitochondrial matrix is determined to be the most enriched GO term of the cellular component (CC).

LASSO regression analysis is an algorithm to filter variates by calculating λ with the smallest classification error. SVM-RFE is also an algorithm utilised to determine comfortable variates by subtracting the feature vectors generated by SVM based on support vector machines. Both LASSO and SVM-RFE were applied to screen potential diagnostic biomarkers from the 537 differentially expressed metabolism-associated genes. By intersecting the results of LASSO and SVM-RFE, we obtained 6 hub genes, they were CHST13, ETNK1, LPCAT1, PDE6A, PLA2G2A, and UGT2A3, among which LPCAT1 and PLA2G2A were determined to be significantly overexpressed in UC while the other 4 were significantly downregulated in UC. The capability of aberrant expression for each of the hub genes was verified in the test cohort. PLA2G2A showed the weakest diagnostic capability, with AUC = 0.624, and UGT2A3 showed the strongest diagnostic capability, with AUC = 0.856. PLA2G2A, a phospholipase, has been reported to engage in pancreatic cancer immune escape [25], excessive lipid peroxidation [26], steatotic liver disease [27], and phenotypes of several cancers [28]. It is worth mentioning that PLA2G2A is reported to upregulate in intestinal cancers and is summarised as a susceptible gene possibly driven as downstream of inflammatory signals (IL-1, IL-6, TNF-α, and IFN-γ) [29], which may co-harboured by UC. Several previous studies have mentioned the upregulation of PLA2G2A during UC development, but the molecular mechanisms in the depth and diagnostic value of PLA2G2A have not been explored further [30, 31].

Thus, we present the first study to report the diagnostic value of PLA2G2A in UC. UGT2A3, a member of the UDP glucuronosyltransferase family, has been observed to represent the strongest process toward the goal of having a complete set of recombinant human UGTs for comparative functional analyses [32]. UGT2A3 was also reported to associate with colon cancer progression [33] and bile acid level [34]. A previous study reported upregulation of UGT2A3 isoforms in long-duration UC, which conflicted with our observation, possibly resulting from their small cohort with limited samples (32 colonic biopsies) [35]. To the best of our knowledge, no studies have revealed the diagnostic value of UGT2A3 in UC previously. As for the other 4 hub genes (CHST13, ETNK1, LPCAT1, and PDE6A), their diagnostic roles in UC were reported for the first time in our present study, while the main functional characterisation of the 4 hub genes have been clarified backgrounded by other non-UC diseases. CHST13, a carbohydrate sulfotransferase, has mainly been reported to associate with survival of patients with gastrointestinal cancer via impacting the metabolism of abnormal bile acids [36]. ETNK1, an ethanolamine kinase, has mutation mainly correlated with haematological malignancies [37, 38]. LPCAT1, a lysophosphatidylcholine acyltransferase, was reported to promote Crohn's disease progression via the release of epithelial-mesenchymal transition [39]. It is feasible that the mechanisms mentioned above involving the other 4 hub genes may also be employed to participate in UC pathogenesis.

CIBERSORT is a robust public database for immune infiltration analysis, with the aid of which we managed to determine immune cell infiltration patterns in UC. We assessed higher abundance of B cells memory, T cells CD4 memory activated, T cells follicular helper, NK cells resting, macrophages M0, macrophages M1, dendritic cells activated, mast cells activated, and neutrophils in UC compared to the normal, which may indicate the potential engagement of these immune cells in UC development and immune response. Th17/Tregs balance appears to exert a pivotal influence on gut immunity of UC [40]. A study reported that after silencing mTOR, the levels of HIF-1α and cellular glycolysis decrease, Th17 cell differentiation decreases, pro-inflammatory cytokine levels decrease, and anti-inflammatory cytokine levels increase in UC [17]. Interestingly, a previous study examined the HRas dependent mechanism of disruption of balance between regulatory Tregs and Th17 in UC [41]. The above research, together with our results, reveal that several immune cells are particularly recruited in UC development, such as Th17 cells and Tregs, while most of the other immune cells remain computationally predicted. The detailed mechanisms await further exploration, especially with experimental evidence.

In terms of immune correlation analysis of the 6 diagnostic biomarkers, we found that the upregulated ones showed totally different correlation with immune cells compared with downregulated ones. B cells memory, T cells CD4 memory activated, dendritic cells activated, macrophages M0, macrophages M1, mast cells activated, and neutrophils were all significantly positively correlated with LPCAT1 and PLA2G2A, the 2 upregulated diagnostic biomarkers in UC. Mast cells resting, NK cells activated, and macrophages M2 were the principal immune cells that significantly positively correlated with the other 4 downregulated diagnostic biomarkers (CHST13, ETNK1, LPCAT1, and PDE6A). However, no previous studies have reported the correlation between our present 6 diagnostic biomarkers and diverse immune cells; hence, there is still a lot of work remaining.

Conclusions

In the present study we appraised 6 genes (*CHST13*, *ETNK1*, *LPCAT1*, *PDE6A*, *PLA2G2A*, and *UGT2A3*) as potential valuable diagnostic biomarkers for UC by utilising LASSO regression analysis and SVM-RFE. The robust diagnostic value of the 6 metabolism-related biomarkers were demonstrated with the ROC curve and verified in the test cohort. Infiltration patterns of immune cells in UC were assessed, and the exact correlation between 6 diagnostic biomarkers and diverse immune cells were determined for the first time.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Gros B, Kaplan GG. Ulcerative Colitis in Adults: A Review. JAMA 2023; 330: 951-965.
2. Syed S, Boland BS, Bourke LT, et al. Challenges in IBD Research 2024: Precision Medicine. Inflamm Bowel Dis 2024; 30 (Suppl 2): S39-S54.
3. Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. Lancet 2023; 402: 571-584.
4. Honap S, Jairath V, Danese S, Peyrin-Biroulet L. Navigating the complexities of drug development for inflammatory bowel disease. Nat Rev Drug Discov 2024; 23: 546-562.
5. Neurath MF, Vieth M. Different levels of healing in inflammatory bowel diseases: mucosal, histological, transmural, barrier and complete healing. Gut 2023; 72: 2164-2183.
6. Honap S, Jairath V, Sands BE, Dulai PS, Danese S, Peyrin-Biroulet L. Acute severe ulcerative colitis trials: the past, the present and the future. Gut 2024; 73: 1763-1773.
7. Fang X, Ardehali H, Min J, Wang F. The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nat Rev Cardiol 2023; 20: 7-23.
8. Faqerah N, Walker D, Gerasimidis K. Review article: The complex interplay between diet and Escherichia coli in inflammatory bowel disease. Aliment Pharmacol Ther 2023; 58: 984-1004.

9. Guo J, Li L, Cai Y, Kang Y. The development of probiotics and prebiotics therapy to ulcerative colitis: a therapy that has gained considerable momentum. Cell Commun Signal 2024; 22: 268.
10. Yang Y, Xiao G, Cheng P, Zeng J, Liu Y. Protective Application of Chinese Herbal Compounds and Formulae in Intestinal Inflammation in Humans and Animals. Molecules 2023; 28: 6811.
11. Zhang X, Zhang B, Peng B, et al. Different Dose of Sucrose Consumption Divergently Influences Gut Microbiota and PPAR-γ/MAPK/NF-κB Pathway in DSS-Induced Colitis Mice. Nutrients 2022; 14: 2765.
12. Long D, Mao C, Huang Y, Xu Y, Zhu Y. Ferroptosis in ulcerative colitis: Potential mechanisms and promising therapeutic targets. Biomed Pharmacother 2024; 175: 116722.
13. Peng S, Shen L, Yu X, et al. The role of Nrf2 in the pathogenesis and treatment of ulcerative colitis. Front Immunol 2023; 14: 1200111.
14. Li J, Luo X, Shiu PH, et al. Protective effects of Amauroderma rugosum on dextran sulfate sodium-induced ulcerative colitis through the regulation of macrophage polarization and suppression of oxidative stress. Biomed Pharmacother 2024; 176: 116901.
15. Bourgonje AR, Kloska D, Grochot-Przeczek A, Feelisch M, Cuadrado A, van Goor H Personalized redox medicine in inflammatory bowel diseases: an emerging role for HIF-1alpha and NRF2 as therapeutic targets. Redox Biol 2023; 60: 102603.
16. He N, Chen K, Yu S, et al. Stachyose Exerts Anticolitis Efficacy by Re-balancing Treg/Th17 and Activating the Butyrate-Derived PPARgamma Signaling Pathway. J Agric Food Chem 2024; 72: 12171-12183.
17. Wang Y, Li M, Zha A. mTOR promotes an inflammatory response through the HIF1 signaling pathway in ulcerative colitis. Int Immunopharmacol 2024; 134: 112217.
18. Riviere P, Li Wai Suen C, Chaparro M, De Cruz P, Spinelli A, Laharie D. Acute severe ulcerative colitis management: unanswered questions and latest insights. Lancet Gastroenterol Hepatol 2024; 9: 251-262.
19. Thorp EB, Karlstaedt A. Intersection of Immunology and Metabolism in Myocardial Disease. Circ Res 2024; 134: 1824-1840.
20. Wang X, Zhang C, Zhao G, Yang K, Tao L. Obesity and lipid metabolism in the development of osteoporosis (Review). Int J Mol Med 2024; 54: 61.
21. Dankar R, Wehbi J, Refaat MM. Tailoring Treatment in Cardiovascular Diseases: The Role of Targeted Therapies. Pharmaceutics 2024; 16: 461.
22. Yamaji T, Hanada K. Sphingolipid metabolism and interorganellar transport: localization of sphingolipid enzymes and lipid transfer proteins. Traffic 2015; 16: 101-122.
23. Bayoumy AB, Mulder CJJ, Ansari AR, et al. Uphill battle: Innovation of thiopurine therapy in global inflammatory bowel disease care. Indian J Gastroenterol 2024; 43: 36-47.
24. Shi F, Gao YS, Han SM, et al. Allulose mitigates chronic enteritis by reducing mitochondria dysfunction via regulating cathepsin B production. Int Immunopharmacol 2024; 129: 111645.
25. Ge W, Yue M, Lin R, et al. PLA2G2A(+) cancer-associated fibroblasts mediate pancreatic cancer immune escape via impeding antitumor immune response of CD8(+) cytotoxic T cells. Cancer Lett 2023; 558: 216095.
26. Huang X, Yang X, Zhang M, et al. SELENOI Functions as a Key Modulator of Ferroptosis Pathway in Colitis and Colorectal Cancer. Adv Sci (Weinh) 2024; 2024: e2404073.
27. Sasidharan K, Caddeo A, Jamialahmadi O, et al. IL32 downregulation lowers triglycerides and type I collagen in di-lineage human primary liver organoids. Cell Rep Med 2024; 5: 101352.
28. Hatori S, Sakamaki K, Yokohori T, et al. Clinical Significance of PLA2G2A Expression in Gastric Cancer Patients who Receive Gastrectomy and Adjuvant S-1. Anticancer Res 2021; 41: 3583-3588.
29. Fijneman RJ, Cormier RT. The roles of sPLA2-IIA (Pla2g2a) in cancer of the small and large intestine. Front Biosci 2008; 13: 4144-4174.
30. Ding X, Yan F, Wang W, Qin J, Luo L. Integration of transcriptomics and metabolomics identify biomarkers of aberrant lipid metabolism in ulcerative colitis. Int Immunopharmacol 2024; 131: 111865.
31. Escudero-Hernández C, van Beelen Granlund A, Bruland T, et al. Transcriptomic Profiling of Collagenous Colitis Identifies Hallmarks of Nondestructive Inflammatory Bowel Disease. Cell Mol Gastroenterol Hepatol 2021; 12: 665-687.
32. Court MH, Hazarika S, Krishnaswamy S, Finel M, Williams JA. Novel polymorphic human UDP-glucuronosyltransferase 2A3: cloning, functional characterization of enzyme variants, comparative tissue expression, and gene induction. Mol Pharmacol 2008; 74: 744-754.
33. Wu H, Zhong W, Zhang R, et al. G-quadruplex-enhanced circular single-stranded DNA (G4-CSSD) adsorption of miRNA to inhibit colon cancer progression. Cancer Med 2023; 12: 9774-9787.
34. Yang X, Li P, Zhuang J, et al. Identification of Molecular Targets of Bile Acids Acting on Colorectal Cancer and Their Correlation with Immunity. Dig Dis Sci 2024; 69: 123-134.
35. Low END, Mokhtar NM, Wong Z, Raja Ali RA. Colonic Mucosal Transcriptomic Changes in Patients with Long-Duration Ulcerative Colitis Revealed Colitis-Associated Cancer Pathways. J Crohns Colitis 2019; 13: 755-763.
36. Wu X, Liu P, Wang Q, Sun L, Wang Y. A prognostic model established using bile acid genes to predict the immunity and survival of patients with gastrointestinal cancer. Environ Toxicol. 2024. doi: 10.1002/tox.24287.
37. Szuber N, Orazi A, Tefferi A. Chronic neutrophilic leukemia and atypical chronic myeloid leukemia: 2024 update on diagnosis, genetics, risk stratification, and management. Am J Hematol 2024; 99: 1360-1387.
38. Lang W, Luo Y, Wang L, et al. The der(1;7)(q10;p10) defining a distinct profile from -7/del(7q) in myelodysplastic syndromes: A systematic review and meta-analysis. Cancer Med 2024; 13: e6890.
39. Chen W, Xu Z, Jiang J, et al. Identification of LPCAT1 as a key biomarker for Crohn's disease based on bioinformatics and machine learnings and experimental verification. Gene. 2024; 920: 148519.
40. Hu Y, Tang J, Xie Y, et al. Gegen Qinlian decoction ameliorates TNBS-induced ulcerative colitis by regulating Th2/Th1 and Tregs/Th17 cells balance, inhibiting NLRP3 inflammasome activation and reshaping gut microbiota. J Ethnopharmacol 2024; 328: 117956.
41. Wang S, Su W, Wu X, Dong W. Restoring Treg/Th17 cell balance in ulcerative colitis through HRas silencing and MAPK pathway inhibition. Int Immunopharmacol 2024; 130: 111608.

Adress for correspondence

Yuanyuan Ding
Department of Gastroenterology,
Jining No. 1 People's Hospital,
Jining, China
e-mail: yfqh168vip@163.com

Xiaoming Xu
Department of Gastroenterology,
Jining No. 1 People's Hospital,
Jining, China
e-mail: xuxm9527@163.com