



OPEN Disulfidptosis links the pathophysiology of ulcerative colitis and immune infiltration in colon adenocarcinoma

Chenhao Jiang^{1,3}, Teng Yue^{2,3}, Ziyao Jia^{1,3}, Lili Song^{1,3}, Xiaohang Zeng¹, Ziyu Bao¹, Xinying Li¹, Zhuang Cui², Wenyi Mi^{1✉} & Qianqian Li^{1✉}

Ulcerative colitis (UC), a chronic inflammatory bowel disease, significantly increases the risk of colon adenocarcinoma (COAD). Disulfidptosis, a novel form of programmed cell death, has been implicated in various diseases, including UC. This study investigates the expression of disulfidptosis-related genes, particularly CD2AP and MYH10, in UC and COAD. Through analysis of public datasets, we found MYH10 significantly upregulated and CD2AP downregulated in UC compared to healthy controls, with consistent patterns in COAD. Immune infiltration analysis revealed correlations between these genes and specific immune cell types, suggesting their roles in immune modulation. Molecular docking showed strong binding affinities of UC drugs such as budesonide and sulfasalazine with CD2AP and MYH10. Connectivity Map analysis identified additional drug candidates, including simvastatin and mephenytoin, which may be repurposed for UC and COAD therapy. These findings suggest disulfidptosis-related genes as potential biomarkers and therapeutic targets, linking chronic inflammation to cancer progression.

Keywords Disulfidptosis, CD2AP, MYH10, Ulcerative colitis, Colon adenocarcinoma, Drug repurposing

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by inflammation and ulceration of the colon and rectum¹. Its global incidence is increasing, particularly in newly industrialized countries adopting Western lifestyles². Symptoms such as bloody diarrhea, abdominal pain, urgency to defecate, and weight loss significantly affect patients' quality of life^{3,4}. While its etiology remains unclear, UC likely arises from an abnormal immune response to gut flora in genetically predisposed individuals, with environmental factors, such as diet, stress and microbial composition, contributing to disease onset and progression^{5,6}. Current treatments include anti-inflammatory drugs, immunosuppressants, biologics and lifestyle modifications⁷; however, UC remains a chronic condition.

Continuous inflammation in UC increases the risk of colon adenocarcinoma (COAD), with long-standing inflammation driving a progression from benign colitis to malignancy^{8,9}. Chronic UC-related inflammation leads to epithelial injury, genomic instability and the accumulation of genetic mutation⁹. Dysbiosis and reactive oxygen species further exacerbate the inflammatory environment, promoting carcinogenesis^{10,11}. Early detection of dysplasia through surveillance colonoscopy is vital for preventing COAD in UC patients¹². Understanding the molecular mechanisms underlying the UC-COAD transition is essential for identifying biomarkers and therapeutic targets to mitigate disease progression.

Regulated cell death maintains biological equilibrium, but dysregulation can disrupt homeostasis, exacerbating diseases like UC. Emerging evidence highlights the role of apoptosis, autophagy, pyroptosis and ferroptosis in UC pathology^{13–16}. Disulfidptosis, a newly identified form of programmed cell death associated with oxidative stress, is distinct from apoptosis and ferroptosis. It involves intracellular disulfide accumulation, actin cytoskeleton collapse and cell death, particularly under glucose starvation^{17,18}. UC-associated metabolic conditions, such as glucose depletion¹⁹ and cystine accumulation²⁰, create an environment conducive to disulfidptosis, implicating it in disease progression.

¹Department of Immunology, Key Laboratory of Immune Microenvironment and Disease of the Educational Ministry of China, Tianjin Key Laboratory of Cellular and Molecular Immunology, School of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China. ²Epidemiology and Biostatistics Institute, School of Public Health, Tianjin Medical University, Tianjin 300070, China. ³These authors contributed equally: Chenhao Jiang, Teng Yue, Ziyao Jia and Lili Song. ✉email: wenyi.mi@tmu.edu.cn; qianqianli_2015@126.com

Disulfidptosis, a novel form of programmed cell death triggered by oxidative stress, occurs under glucose starvation in cells with elevated levels of the cystine transporter SLC7A11. Unlike apoptosis or ferroptosis, disulfidptosis is characterized by the accumulation of intracellular disulfides, leading to disulfide stress. This stress induces aberrant disulfide bonding in actin cytoskeleton proteins, causing the collapse of the F-actin network and eventual cell death. SLC7A11 facilitates cystine import, and under glucose-starved conditions, this process depletes NADPH and generates toxic disulfide bonds, culminating in cell death^{17,18}. The metabolic landscape of UC, marked by glucose depletion and cystine accumulation, creates conditions favorable for disulfidptosis^{19,20}. Emerging evidence suggests that modulating this pathway may offer therapeutic benefits. For instance, modified Gegen Qinlian decoction (MGQD) has shown promise in alleviating UC symptoms by targeting disulfidptosis²¹.

In this study, we explored the role of disulfidptosis in the progression of UC and its potential implications for COAD. By analyzing gene expression profiles from multiple publicly available datasets, we identified key disulfidptosis-related genes, particularly CD2AP and MYH10, which exhibited significant differential expression in UC tissues compared to healthy controls. We further examined the involvement of these genes in COAD, revealing consistent changes in their expression patterns across both diseases. To assess their therapeutic potential, we performed molecular docking studies with commonly used UC drugs and identified additional drug candidates through the Connectivity Map (CMAP) tool. The expression of CD2AP and MYH10 was then validated in UC and COAD tissues using immunohistochemistry (IHC). These findings offer novel insights into the role of disulfidptosis in UC and COAD, suggesting that CD2AP and MYH10 could serve as potential biomarkers and therapeutic targets to mitigate disease progression.

Results

Identification of differentially expressed genes associated to disulfidptosis in UC

To identify differentially expressed genes (DEGs) linked to disulfidptosis in UC, we analyzed four publicly available datasets: GSE87473, GSE38713, GSE75214 and GSE92415. Heatmaps were generated to visualize the expression patterns of DEGs in UC samples compared to healthy controls across these datasets (Fig. 1A–D). A Venn diagram was used to identify overlapping DEGs across all four datasets (Fig. 1E).

This analysis revealed seven genes—SLC7A11, NDUFS1, NUBPL, RPN1, CD2AP, MYH10 and PDLIM1—that were dysregulated in all four UC datasets (Fig. 1E and Table S1). Given the inconsistent expression patterns of NDUFS1, we focused our subsequent analysis on six genes with consistent expression profiles: SLC7A11, NUBPL, RPN1, CD2AP, MYH10 and PDLIM1. The genomic locations and potential chromosomal hotspots of these genes were visualized in a circular plot (Fig. 1F).

Additionally, to explore the functional relationships among these DEGs, we constructed a protein–protein interaction (PPI) network (Fig. 1G). This analysis revealed significant interactions, particularly between PDLIM1, MYH10 and CD2AP, as well as between NDUFS1 and NUBPL, suggesting that these genes may work together in regulatory pathways implicated in UC.

Correlation analysis of the six hub disulfidptosis related DEGs and immune infiltration

We conducted a correlation analysis to examine the relationship between six disulfidptosis-related genes and various immune functions across four datasets from patients with active UC. Pearson correlation analysis revealed that RPN1 and NUBPL were not significantly associated with any immune cell types or immune functions in the GSE92415 dataset (Fig. 2B), while PDLIM1 showed no significant correlation with immune cells or functions in the GSE38713 dataset (Fig. 2C). In contrast, SLC7A11, CD2AP and MYH10 exhibited significant associations with specific immune cell subtypes and immune functions across multiple datasets, highlighting their potential roles in modulating immune responses in UC (Fig. 2A–D).

Notably, SLC7A11 was strongly positively correlated with activated neutrophils, T helper 1 (Th1) cells and macrophages, suggesting its involvement in immune activation in UC. On the other hand, CD2AP was negatively correlated with several inflammatory immune cell types, implying its role in immune regulation and its potential to reduce the inflammatory environment in UC. MYH10 demonstrated significant correlations with activated dendritic cells (aDCs), Th1 cells and tumor-infiltrating lymphocytes (TILs), further supporting its contribution to the immune response within UC tissues. These findings emphasize the critical roles of SLC7A11, CD2AP and MYH10 in shaping the immune landscape in UC, which plays a central role in disease pathogenesis and progression.

Pathway enrichment and regulatory network analysis of SLC7A11, CD2AP and MYH10 in UC

Analysis of the combined data from the four datasets revealed that SLC7A11 and MYH10 were significantly upregulated in UC samples, while CD2AP was notably downregulated (Figure S1A–C). In the GSE87466 testing dataset, CD2AP expression was significantly downregulated, while MYH10 expression was significantly upregulated in UC tissues compared to normal controls, corroborating our previous findings (Figure S1D).

Ulcerative colitis (UC) is classified into active and inactive stages based on clinical manifestations and disease activity⁵. Furthermore, analysis of the GSE53306 dataset demonstrated that the expression levels of CD2AP and MYH10 were associated with UC disease stages, with CD2AP being significantly downregulated and MYH10 significantly upregulated in active UC tissues compared to inactive UC tissues (Figure S1E).

Gene set enrichment analysis (GSEA) revealed key pathways associated with SLC7A11, CD2AP and MYH10 in UC. Both SLC7A11 and MYH10 were positively enriched in immune-related pathways, such as chemokine signaling, cytokine–cytokine receptor interaction and JAK–STAT signaling, indicating their upregulation in UC samples (Fig. 3A and C). In contrast, CD2AP was negatively enriched, suggesting its downregulation in these immune pathways (Fig. 3B). These results highlight the differential roles of these genes in modulating immune processes in UC.

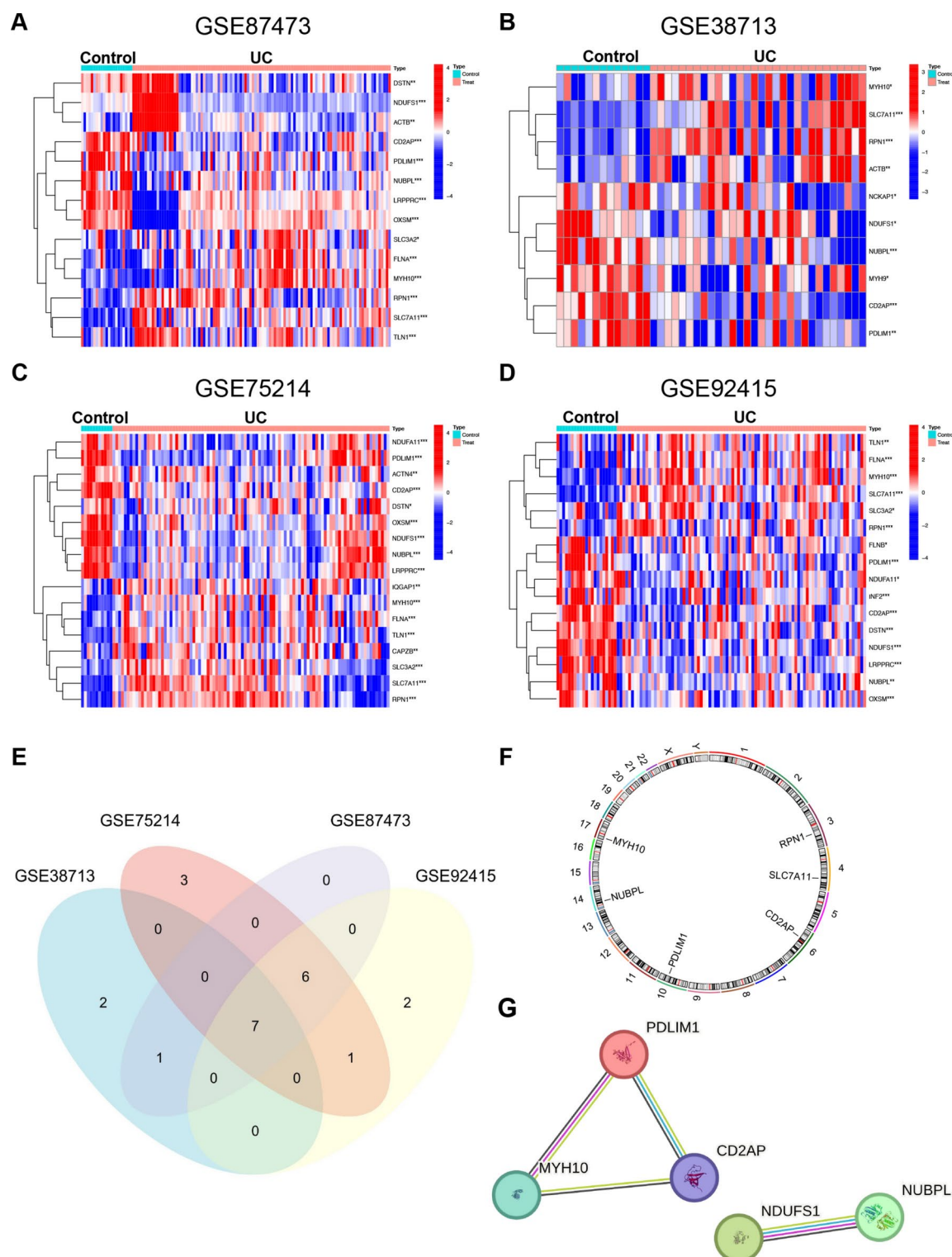


Fig. 1. Differential Expression and Interaction Analysis of Disulfidptosis-Related Genes in UC Across Multiple Datasets. (A–D) Heatmaps showing the expression patterns of differentially expressed genes (DEGs) in UC and control samples across four datasets: GSE87473 (A), GSE38713 (B), GSE75214 (C) and GSE92415 (D). Red indicates upregulation, and blue indicates downregulation. (E) Venn diagram illustrating the overlap of DEGs among the four datasets, highlighting consistently dysregulated genes. (F) Circular plot depicting the genomic locations of six common DEGs, providing insights into their chromosomal distribution. (G) Protein–protein interaction (PPI) network visualizing functional relationships among DEGs, suggesting potential regulatory pathways involved in UC. All results were generated with the R software (version: 4.3.1).

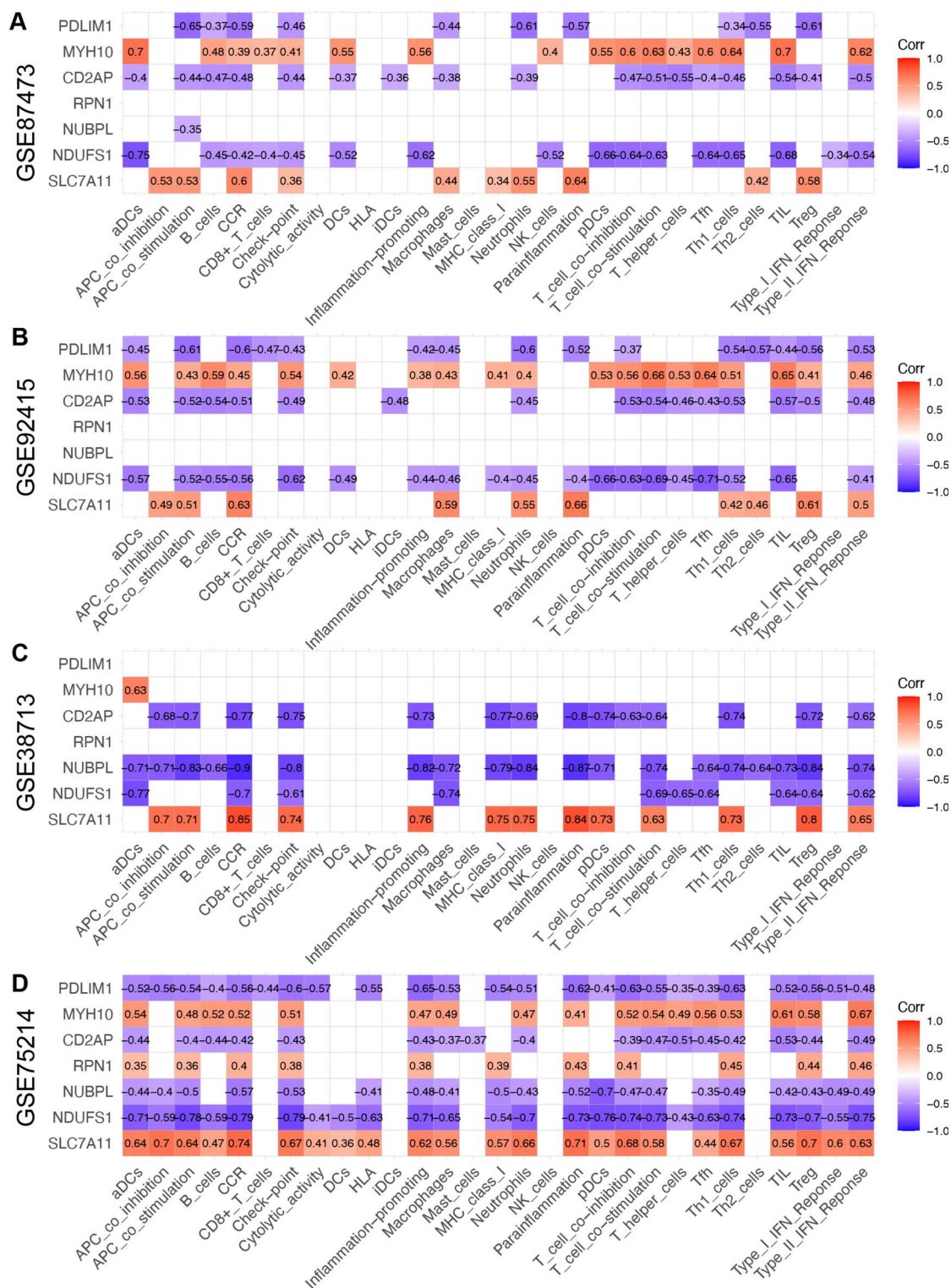


Fig. 2. Correlation Heatmaps of Disulfidptosis-Related Genes with Immune Cell Infiltration in UC Across Four Datasets. Correlation heatmaps showing relationships between disulfidptosis-related genes (PDLIM1, MYH10, CD2AP, RPN1, NUBPL, NDUFS1 and SLC7A11) and immune cell types and immune function in UC samples across four datasets: (A) GSE87473, (B) GSE92415, (C) GSE38713 and (D) GSE75214. All results were generated with the R software (version: 4.3.1).

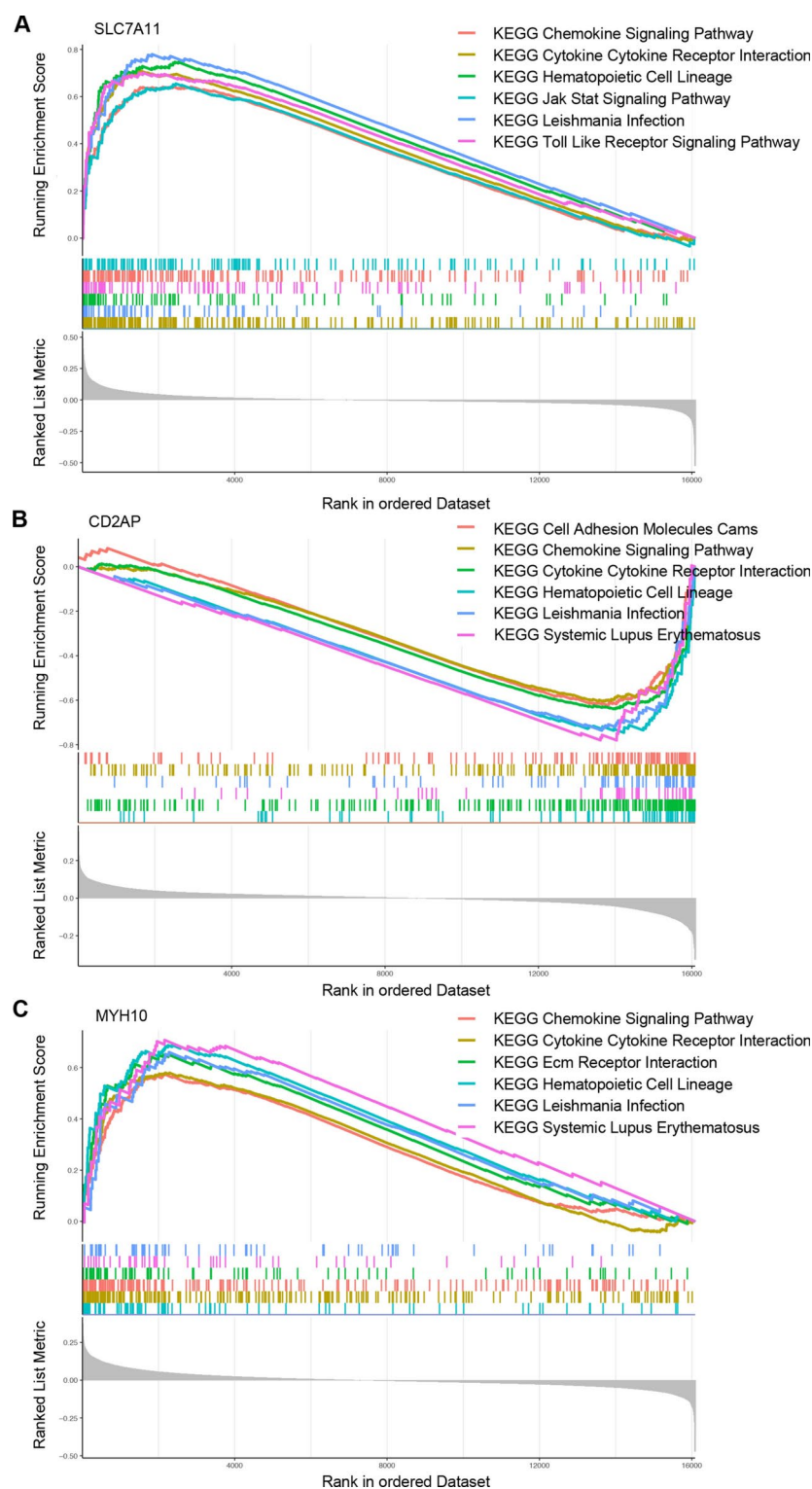


Fig. 3. Pathway Enrichment and Regulatory Network Analysis of SLC7A11, CD2AP and MYH10 in UC. C) GSEA results showing significant pathways associated with SLC7A11 (A), CD2AP (B) and MYH10 (C) in UC. Pathways were analyzed using the KEGG database^{43–45}.

Network analysis further revealed interactions between SLC7A11, CD2AP, MYH10 and various transcription factors or miRNAs. The miRNA regulatory network (Fig. 4A) identified several miRNAs, including hsa-miR-92b-3p, which targets all three genes, suggesting significant post-transcriptional regulation in UC. The transcription factor network (Fig. 4B) highlighted key regulators such as ATF4, PLA1 and YY1 for MYH10 and CD2AP, and HNF1A and YY1 for SLC7A11 and CD2AP.

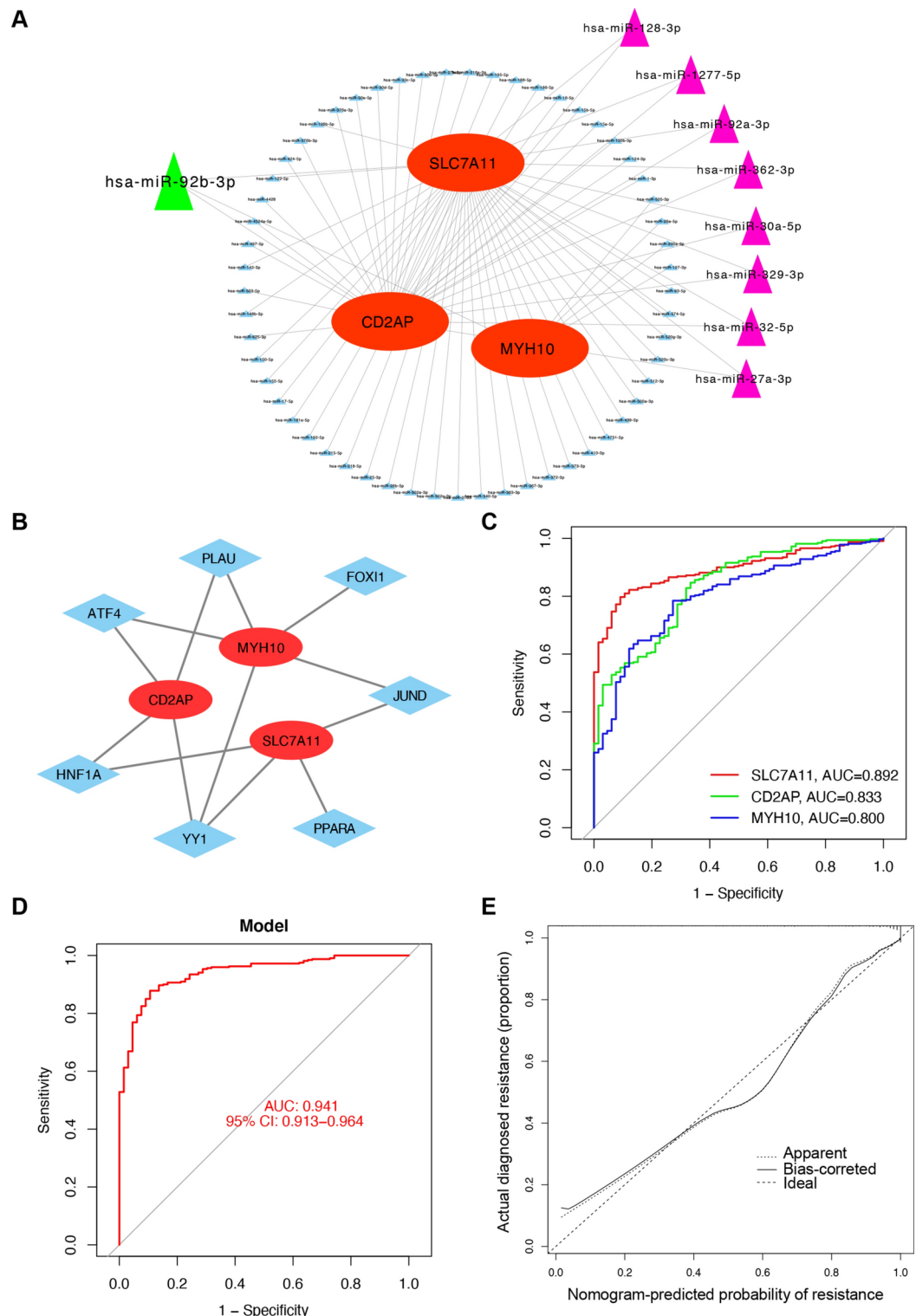


Fig. 4. Regulatory Network Analysis and Diagnostic Performance of Immune-Related Disulfidptosis Genes in UC. (A) miRNA regulatory network for SLC7A11, CD2AP and MYH10. (B) Transcription factor (TF) regulatory network for SLC7A11, CD2AP and MYH10. (C) ROC curves showing diagnostic performance for SLC7A11 (red), CD2AP (green) and MYH10 (blue) in UC. (D) Combined ROC curve for SLC7A11, CD2AP and MYH10, with an AUC of 0.941 (95% CI 0.913–0.964). (E) Calibration curve of the combined diagnostic model for UC.

Diagnostic performance and calibration of SLC7A11, CD2AP and MYH10 in UC

The diagnostic performance of SLC7A11, CD2AP and MYH10 for UC was assessed using receiver operating characteristic (ROC) curve analysis. Each gene individually demonstrated high diagnostic accuracy, with SLC7A11 (red line) showing the highest area under the curve (AUC), followed by CD2AP (green line) and MYH10 (blue line) (Fig. 4C). When combined into a single model, the AUC increased to 0.941, with a 95% confidence interval (CI) of 0.913–0.964, indicating excellent diagnostic ability to differentiate UC patients from normal controls (Fig. 4D). These findings suggest that SLC7A11, CD2AP and MYH10, both individually and as part of a combined model, are effective biomarkers for distinguishing UC from normal tissues. Furthermore, the calibration curve for the combined diagnostic model closely approximated the ideal model, further supporting its reliability and predictive value (Fig. 4E).

CD2AP and MYH10 expression in mouse and human colonic tissues with colitis

SLC7A11 has been established as a key mediator in colitis, regulating ferroptosis through cystine uptake and glutathione synthesis, thereby protecting intestinal epithelial cells from oxidative stress²². Dysregulation of SLC7A11 increases susceptibility to ferroptosis, worsening mucosal damage and inflammation in colitis patients²³. In this study, we focused on investigating the expression patterns of CD2AP and MYH10 in both DSS-induced colitis mouse models and human UC tissues. Western blot analysis revealed a significant reduction in CD2AP expression in the DSS-treated group compared with the control group, whereas MYH10 expression was markedly elevated in the DSS-treated group (Fig. 5A). Immunohistochemistry (IHC) analysis further showed strong expression of CD2AP in control mouse colon tissues, which was significantly diminished in DSS-treated inflammatory tissues (Fig. 5B). Similarly, CD2AP expression was notably lower in UC patient tissues compared to normal tissues (Fig. 5D). In contrast, MYH10 expression was increased in both DSS-treated mouse tissues and UC patient tissues when compared with their respective controls (Fig. 5C, E). Quantitative analysis of IHC staining intensity confirmed the significant downregulation of CD2AP and upregulation of MYH10, particularly in human UC tissues.

These findings underscore the differential expression of CD2AP and MYH10 in DSS-induced colitis and UC tissues, suggesting their crucial roles in the pathogenesis and progression of ulcerative colitis.

Expression patterns and immune cell infiltration of CD2AP and MYH10 in COAD

The expression of CD2AP and MYH10 in normal and COAD tissues was analyzed using TCGA data. This revealed that CD2AP mRNA levels were significantly higher in normal colon tissues, whereas MYH10 levels were elevated in cancer tissues (Fig. 6A, B). IHC data from the Human Protein Atlas further supported these findings, showing reduced CD2AP and increased MYH10 protein levels in COAD tissues compared to normal tissues (Fig. 6C, D).

The altered expression patterns of CD2AP and MYH10 suggest their potential as prognostic markers in COAD, prompting further exploration of their associations with patient survival outcomes. High CD2AP expression was significantly linked to improved overall survival (OS) and disease-specific survival (DSS, referring to survival outcomes) (Figure S2A and S2B), but not with progress free interval (PFI) (Figure S2C). In contrast, high MYH10 expression was significantly associated with poorer PFI (Figure S2F) and showed a non-significant trend towards worse OS and DSS (referring to survival outcomes) (Figure S2D and S2E).

To investigate the potential role of MYH10 in the tumor microenvironment (TME), we analyzed the stromal, immune and ESTIMATE scores, as well as immune cell infiltration. CD2AP expression showed a significant positive correlation with immune cells, such as T memory cells, T helper 2 cells (Th2) and macrophages (Fig. 7A). In contrast, CD2AP expression was negatively correlated with immune cell types like NK cells, Th17 cells, Tregs and DCs (Fig. 7A). MYH10 expression, on the other hand, was strongly positively correlated with macrophages, NK cells, neutrophils and T memory cells (Fig. 7B), suggesting its involvement in modulating the immune landscape in COAD.

Further analysis of immune cell infiltration revealed significant differences in immune cell levels between high- and low-expression groups of CD2AP and MYH10, underscoring their roles in shaping the immune microenvironment of COAD (Fig. 7C, D). High CD2AP expression was associated with an increased stromal score (Fig. 7E). Notably, the stromal, immune and ESTIMATE scores were significantly higher in the high MYH10 expression group compared to the low-expression group, indicating a more active TME in these patients (Fig. 7F). Figure S2G and S2H show immune cell types that did not exhibit significant differences between the high- and low-expression groups for CD2AP and MYH10.

These results suggest that CD2AP and MYH10 are critical modulators of immune cell infiltration in COAD and may play a key role in mediating interactions between the tumor and the immune system.

Molecular docking and drug prediction analysis targeting CD2AP and MYH10 for UC and COAD therapy

Table S2 lists commonly used drugs for UC treatment²⁴, which were subjected to molecular docking with the disulfidptosis-related genes CD2AP and MYH10, as detailed in Tables S3 and S4. The top three drugs with the highest binding affinities for CD2AP were budesonide (Fig. 8A), sulfasalazine (Fig. 8B) and prednisone (Fig. 8C), while the top drugs for MYH10 were sulfasalazine (Fig. 8D), budesonide (Fig. 8E) and hydrocortisone (Fig. 8F). These results suggest that these drugs may effectively target CD2AP and MYH10, indicating potential therapeutic benefits for UC treatment.

Additionally, the CMAP tool was used to identify drugs that may target genes significantly associated with CD2AP and MYH10 for the treatment of UC or COAD. Table S5 lists the top 10 predicted drugs in colon cancer cell lines (SW480, HCT116 and HT29). Molecular docking studies revealed strong binding affinities of CD2AP with simvastatin (Fig. 8G) and mephenytoin (Fig. 8H), and of MYH10 with simvastatin (Fig. 8I)

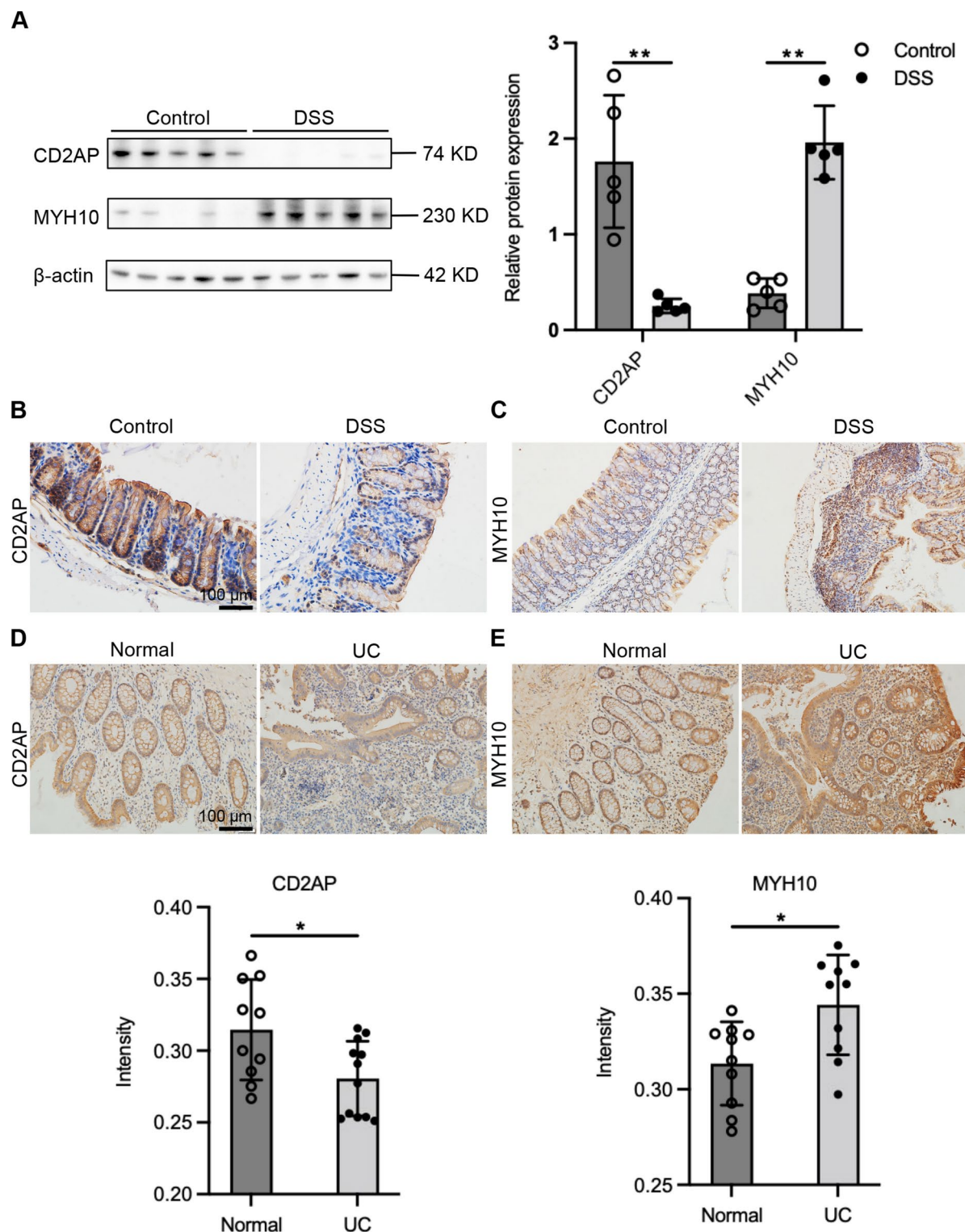


Fig. 5. Expression Analysis of Immune-Related Disulfidptosis Genes in UC. (A) Western blot bands and quantitative analysis of CD2AP and MYH10 in colon tissues from control and DSS-treated mice, using β-actin as a loading control. Original blots are shown in Supplementary Figure S3. (B, C) IHC analysis of CD2AP (B) and MYH10 (C) expression in colon tissues from control and DSS-treated mice. (D, E) Representative IHC images and quantification of CD2AP (D) and MYH10 (E) expression in colon tissues from normal individuals and UC patients. Quantification was based on five samples, with two or three fields per sample analyzed. Statistical significance: * $p < 0.05$ compared to normal.

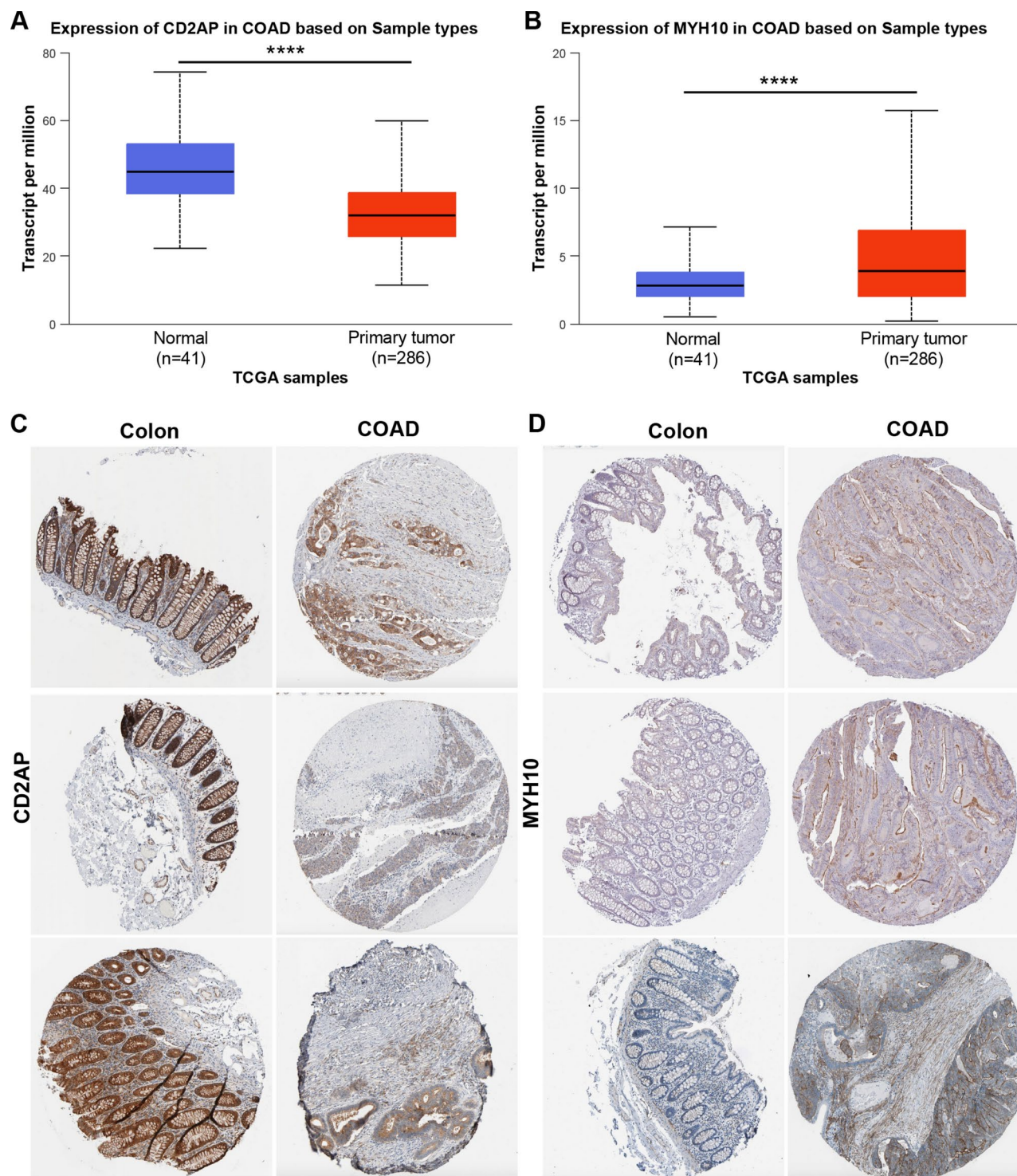


Fig. 6. Expression of CD2AP and MYH10 in Normal Colon and COAD. **(A)** mRNA expression of CD2AP in normal colon (n = 41) and primary COAD tissues (n = 286). **(B)** MYH10 mRNA expression in normal colon (n = 41) and primary COAD tissues (n = 286). **(C, D)** Validation of CD2AP and MYH10 protein expression using the Human Protein Atlas database. IHC images depict protein expression in normal colon versus COAD tissues. Statistical significance: * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$.

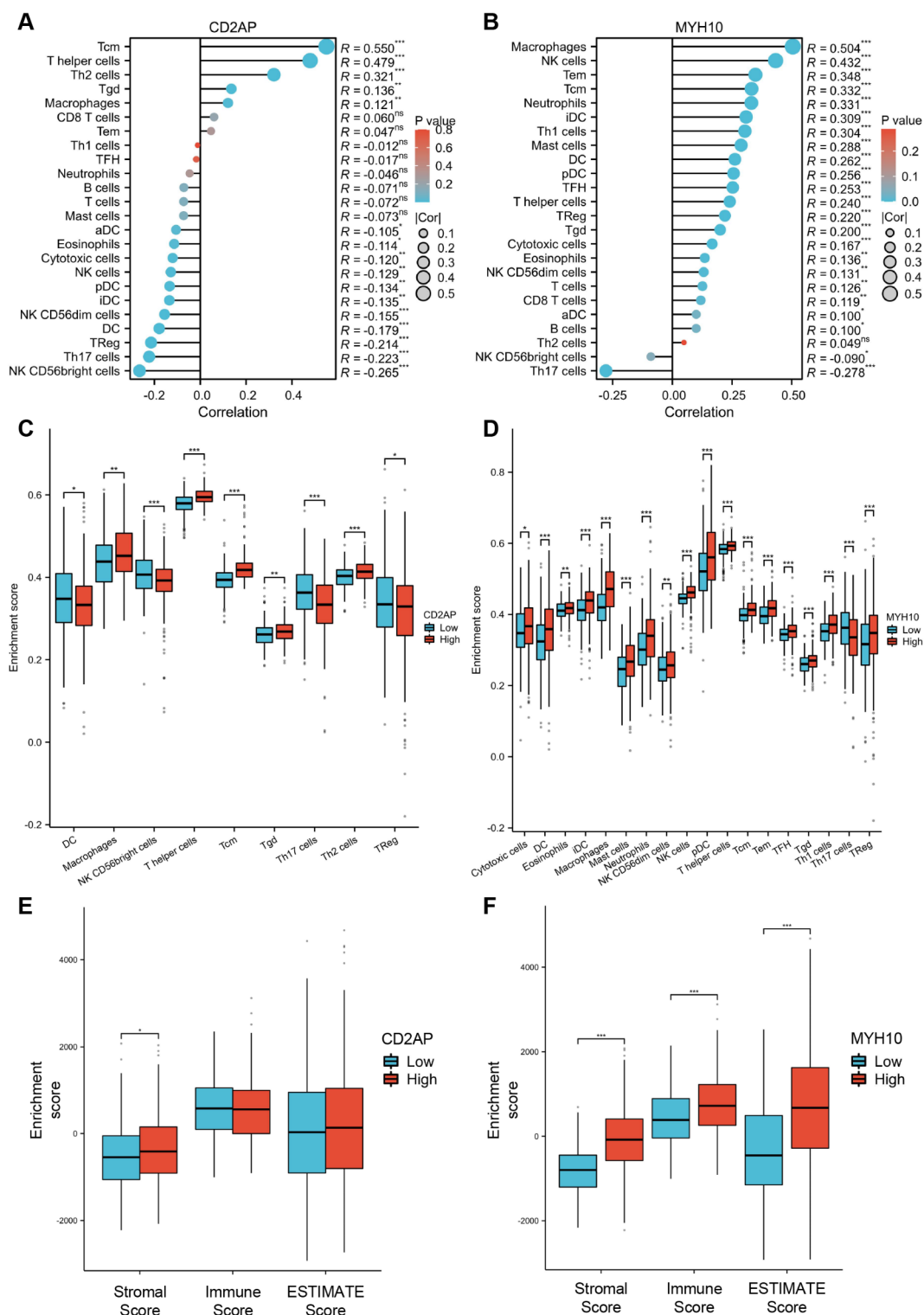


Fig. 7. Correlation and Immune Infiltration Analysis of CD2AP and MYH10 in COAD. (A, B) Correlations between CD2AP (A) and MYH10 (B) expression with immune cell types in COAD, illustrating associations with different immune populations. (C, D) Immune cell infiltration levels in COAD patients with low and high expression of CD2AP (C) or MYH10 (D). (E, F) Stromal score, immune score and ESTIMATE score in COAD patients with low and high expression of CD2AP (E) and MYH10 (F). Statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

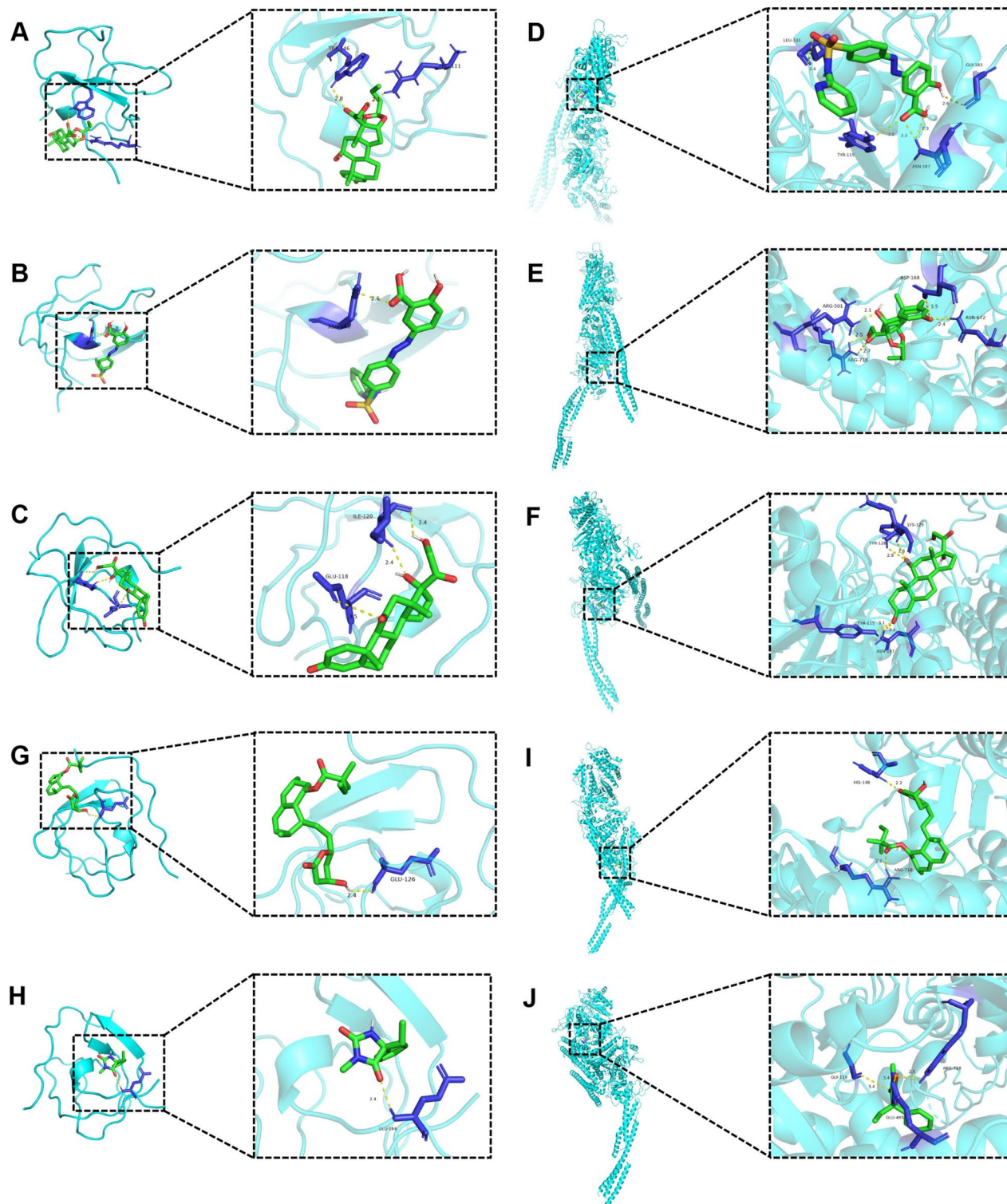


Fig. 8. Molecular Docking and Drug Prediction for UC and COAD Therapy. (A–C) Molecular docking of CD2AP with UC drugs: budesonide (A), sulfasalazine (B) and prednisone (C). (D–F) Molecular docking of MYH10 with UC drugs: sulfasalazine (D), budesonide (E) and hydrocortisone (F). (G, H) Docking of CD2AP with simvastatin (G) and mephenytoin (H). (I, J) Docking of MYH10 with simvastatin (I) and mephenytoin (J). CMAP predictions for drugs targeting CD2AP and MYH10 in colon cancer cell lines SW480, HCT116, and HT29 suggest potential therapeutic applications.

and mephenytoin (Fig. 8J). The strong inverse correlations and high binding affinities suggest that these drugs could be repurposed for the treatment of UC and COAD. These findings highlight the potential of combining molecular docking with drug prediction analyses to identify novel therapeutic strategies for complex diseases.

Discussion

This study investigated the expression and role of disulfidptosis-related genes, CD2AP and MYH10, in the pathogenesis of UC and COAD. Analysis of four publicly available UC datasets identified six consistently dysregulated genes: SLC7A11, NUBPL, RPN1, CD2AP, MYH10 and PDLIM1. Among these, SLC7A11, CD2AP and MYH10 were prioritized for further analysis due to their significant correlations with immune cells. Our results demonstrated that CD2AP expression was significantly reduced, whereas MYH10 expression was markedly increased in DSS-treated mice and UC patients compared to healthy controls.

Extending this analysis to COAD revealed that CD2AP and MYH10, which are significantly dysregulated in UC, also exhibit altered expression in COAD. The consistent downregulation of CD2AP and upregulation of MYH10 in COAD tissues suggest their involvement in the progression from chronic inflammation to cancer. These findings enhance our understanding of the molecular pathways linking UC and COAD and propose these genes as potential molecular bridges between inflammation and malignancy.

SLC7A11 plays a critical role in inflammatory diseases such as UC by regulating cystine uptake and glutathione synthesis, which maintain redox balance and protect against oxidative stress²⁵. Our findings align with prior studies showing upregulation of SLC7A11 in UC, likely as a compensatory response to oxidative damage. This upregulation is also associated with increased immune activation, identifying SLC7A11 as a pivotal factor in UC pathogenesis and a promising therapeutic target. In COAD, SLC7A11 promotes cancer progression by facilitating cystine uptake and glutathione biosynthesis, thereby protecting cancer cells from oxidative stress and ferroptosis. It also modulates immune responses and is associated with microsatellite instability, reinforcing its potential as a therapeutic target²⁶.

CD2AP is a scaffolding protein essential for actin cytoskeleton organization, maintaining cell shape, and facilitating intracellular signaling²⁷. In immune cells, particularly T cells, CD2AP is critical for forming immunological synapses by orchestrating receptor patterning and establishing cytoskeletal polarity, which are necessary for effective immune responses²⁸. Its role in endocytosis further supports the internalization and processing of surface receptors, modulating immune cell activity²⁹. Reduced CD2AP expression in UC colonic tissues indicates disruption of these cellular processes. This downregulation likely contributes to impaired barrier function, increased translocation of luminal antigens and microbes, and exacerbation of inflammation. Similarly, in COAD, reduced CD2AP disrupts cellular architecture and signaling pathways, facilitating tumor invasion and metastasis by weakening cell adhesion and enhancing motility. The observed negative correlation between CD2AP and immune cells such as Tregs suggests that its reduced expression may weaken immune responses, creating a permissive environment for tumor progression³⁰.

MYH10, a nonmuscle myosin heavy chain, is pivotal for maintaining cell structure and motility by regulating actin-myosin contractility³¹. In cancer, MYH10 facilitates epithelial-mesenchymal transition (EMT), supports invasive behavior through cytoskeletal reorganization, and contributes to cytokinesis, with dysregulation potentially leading to aneuploidy—a hallmark of tumor cells^{32,33}. Our findings showed marked upregulation of MYH10 in UC tissues, a phenomenon not extensively studied in colitis. Increased MYH10 expression may enhance migratory and proliferative capacities of immune cells in inflamed colonic mucosa, suggesting its role in cytoskeletal reorganization that supports chronic inflammation in UC. Additionally, in COAD, MYH10 upregulation likely contributes to invasive properties of cancer cells by promoting cytoskeletal rearrangements. The observed increases in stromal, immune and ESTIMATE scores in patients with high MYH10 expression suggest it fosters a more active, possibly immunosuppressive tumor microenvironment, facilitating tumor growth and immune evasion³⁴.

Comparing our findings with recent studies on disulfidptosis in UC reveals both similarities and distinctions. These studies emphasize the role of disulfidptosis-related genes in UC, identifying genes such as SLC7A11, CD2AP, MYH10, LRPPRC, NDUFS1 and PDLIM1 as key players associated with immune cell infiltration and disease progression^{35–37}. For instance, Jinke Huang examined the therapeutic effects of modified Gegen Qinlian decoction (MGQD) in mediating disulfidptosis to alleviate UC symptoms, identifying MYH10 and FLNA as significant targets²¹.

In contrast to these studies, our research not only identified SLC7A11, CD2AP and MYH10 as significant disulfidptosis-related genes in UC but also extended the analysis to COAD, highlighting their potential role in the transition from chronic inflammation to malignancy. While other studies focused on modulating disulfidptosis through traditional herbal remedies, our work included molecular docking analyses to identify potential small-molecule inhibitors targeting CD2AP and MYH10, offering novel therapeutic strategies for UC and COAD.

Specifically, CMAP analysis identified simvastatin and mephenytoin as promising candidates for repurposing in the treatment of UC and COAD. Simvastatin, a cholesterol-lowering agent with anti-inflammatory properties, has demonstrated efficacy in reducing inflammation and oxidative stress in inflammatory bowel disease, making it a viable candidate for targeting UC and COAD pathways^{38–40}. Mephenytoin, traditionally used as an anticonvulsant, offers novel therapeutic potential by targeting CD2AP and MYH10, providing a dual approach to managing these diseases^{41,42}. The high binding affinities observed in molecular docking studies further support the potential of these drugs in treating UC and COAD.

These findings underscore the dual roles of CD2AP and MYH10 in UC and COAD. CD2AP appears to act as a protective factor by maintaining immune balance and suppressing tumor growth, whereas MYH10 contributes to chronic inflammation and tumor progression by enhancing immune cell infiltration and reshaping the tumor microenvironment. Understanding how these genes influence the progression of UC and COAD, including their roles in modulating immune responses and inflammation, could provide critical insights for developing new

therapeutic strategies. Future efforts should focus on restoring CD2AP function to mitigate inflammation and inhibit tumor growth or targeting MYH10 to modulate the immune microenvironment in both inflammatory and cancerous contexts. As disulfidptosis is a relatively new concept in programmed cell death, further in vitro, in vivo and clinical studies are essential to elucidate its role in IBD and COAD.

Conclusion

This study highlights the critical roles of disulfidptosis-related genes, CD2AP and MYH10, in the development of UC and COAD. Our findings show that CD2AP and MYH10 are differentially expressed in these conditions, with CD2AP potentially acting as a suppressor and MYH10 contributing to inflammation and tumor progression. Analysis of immune cell infiltration associated with these genes revealed their involvement in shaping the tumor microenvironment and inflammatory responses, emphasizing their dual roles in inflammation and cancer. The identification of potential therapeutic targets through CMAP analysis underscores the clinical relevance of these findings. Future research should validate these targets in clinical settings to develop novel strategies for managing UC and COAD by targeting disulfidptosis pathways.

Further investigation is needed to clarify the specific roles of CD2AP and MYH10 in UC and COAD pathogenesis. Exploring the regulatory mechanisms underlying their expression and their interactions with cellular proteins will provide a deeper understanding of their contributions to disease progression. Additionally, assessing the therapeutic potential of targeting these genes could lead to new treatment approaches for UC and COAD, aiming to restore cellular homeostasis and reduce inflammation.

Materials and methods

Data acquisition and DEG analysis

The GSE87473, GSE92415, GSE75214, GSE38714, GSE87466 and GSE53306 datasets were sourced from the GEO database. The GSE87473 dataset included 21 normal samples and 106 UC samples, whereas the GSE92415 dataset included 21 normal samples and 87 UC samples. The GSE75214 dataset included 11 normal samples and 97 UC samples, and the GSE38714 dataset included 13 normal samples and 30 UC samples. The GSE87466 dataset included 21 normal samples and 87 UC samples, and the GSE53306 dataset included 12 inactive UC samples and 16 active UC samples. A total of 24 disulfidptosis-related genes were subsequently identified from a previous report¹⁷. Each dataset was analysed separately for variance via the limma package (version: 3.5) of R software (version: 4.3.1). The screening thresholds were set at $|\log_2FC| > 1$ and $P < 0.05$. Differential analysis results were visualized via heatmaps, which were generated with the R pheatmap package (version: 1.0.12). “VennDiagram” package was applied to visualize the differentially expressed genes. Protein-protein interaction (PPI) networks were constructed via the STRING online database to analyse the functional interactions between proteins. The PPI score threshold was set at 0.15, and all differentially expressed genes (DEGs) involved in protein interactions were included. The gene expression profiles of 521 COAD patients were downloaded from the TCGA through the GDC data portal, and TPM-formatted data were extracted. Data processing was performed via Xiantao academic tools (<https://www.xiantaozi.com/products>). Differential expression analysis was conducted via the online tool UALCAN (<http://ualcan.path.uab.edu/index.html>) to compare identified hub genes between normal and colon cancer tissue samples.

Immune infiltration analysis

Single-sample gene set enrichment analysis (ssGSEA) was used to calculate the infiltration scores of 16 immune cells and the activities of 13 immune-related pathways. The R “ggcorrplot” package was used to conduct Spearman’s rank correlation analysis to illustrate the relationships between hub genes expression levels and the immune status.

Gene set enrichment analysis (GSEA)

GSEA (<http://www.broadinstitute.org/gsea>) was used to identify genes that were differentially expressed between the high- and low-expression groups on the basis of the expression profiles of UC patients. Gene set enrichment analysis (GSEA) was performed to explore the functionally enriched pathways and hallmark gene sets related to subgroups via the clusterProfiler R package. The hallmark (h.all.v7.3) gene sets were downloaded from the Molecular Signatures Database (MSigDB, <http://software.broadinstitute.org/gsea/msigdb/>). The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were analyzed, with KEGG pathways referenced according to Kanehisa et al^{43–45}. After 1000 permutations, enriched gene sets were identified on the basis of a P value < 0.05 and a false discovery rate (FDR) of 0.25.

Identification of transcription factor and miRNA interactions via gene regulatory network construction

Transcription factor (TF) target gene interactions were analysed to identify TFs that bind to genes at regulatory regions. TF target genes were predicted via the Enrichr database (<http://amp.pharm.mssm.edu/Enrichr/>). The results with a p value ≤ 0.05 were chosen as the cut-off values. Target miRNAs of genes were predicted via the miRanda, miRDB and TargetScan databases. To improve the prediction accuracy, only the miRNAs predicted by all three databases were retained. The network was visualized via Cytoscape software (v3.9.0).

Selection and verification of feature genes

To evaluate the ability of the candidate feature genes to distinguish between the control and disease (UC) groups, their expression levels were compared between these groups, and receiver operating characteristic (ROC) curves were plotted for each gene. The pROC package was used to construct ROC curves, and the area under the curve

(AUC) was calculated to assess the predictive value of genes associated with disulfidoptosis. An AUC of less than 0.5 indicates no discrimination, an AUC between 0.7 and 0.8 is considered acceptable, an AUC between 0.8 and 0.9 is deemed excellent, and an AUC above 0.9 is considered outstanding.

Animal treatment and sample collection

Wild-type male C57BL/6 J mice were purchased from the Academy of Military Medical Science (Beijing, China). Male C57BL/6 mice (6–8 weeks old) were divided into control and DSS-treated groups. The DSS group received 2.5% DSS in the drinking water for 7 days to induce colitis, whereas the control group received regular water. DSS treatment was considered successful when the body weight decreased by more than 15%. The mice were anesthetized with ketamine and then euthanized by cervical dislocation, after which colon tissues were collected.

All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Tianjin Medical University. All procedures were carried out in accordance with the relevant institutional guidelines and regulations.

Immunohistochemical analysis

Paraffin-embedded colon tissue sections from normal individuals and colitis patients or control and DSS-treated mice were subjected to immunohistochemical staining. Colon tissues were fixed in 10% neutral-buffered formalin for 24 h and embedded in paraffin. Sections (5 µm thick) were deparaffinized, rehydrated and subjected to antigen retrieval in citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. The sections were incubated overnight at 4 °C with primary antibodies against CD2AP⁴⁶ (24,122-1-AP, Proteintech, Rosemont, IL, USA) and MYH10⁴⁷ (19673-1-AP, Proteintech, Rosemont, IL, USA), followed by incubation with biotinylated secondary antibodies and a streptavidin–horseradish peroxidase complex. The immune complexes were visualized via diaminobenzidine (DAB) and counterstained with hematoxylin. Images were captured under a light microscope.

Human tissue samples were collected with approval from the Ethics Committee of Jinghai Hospital, Tianjin, China. Informed consent was obtained from all participants or their legal guardians, and all procedures were conducted in accordance with the Declaration of Helsinki and institutional ethical guidelines.

Protein extraction and western blot analysis

Colon tissues were homogenized in RIPA lysis buffer with protease and phosphatase inhibitors, sonicated and centrifuged. Protein concentrations were determined via the Bradford assay with Coomassie Brilliant Blue G250 dye. Equal amounts of protein (10 µg) were separated by SDS-PAGE, transferred onto PVDF membranes, and blocked with 5% nonfat dry milk in TBST. The membranes were incubated overnight at 4 °C with primary antibodies against CD2AP and MYH10, followed by incubation with horseradish peroxidase-conjugated secondary antibodies. The protein bands were visualized via an enhanced chemiluminescence (ECL) detection system and quantified via densitometry. The expression levels of CD2AP and MYH10 were compared between the control and DSS-treated groups.

Human protein atlas analysis

The immunohistochemistry expression graph of related genes was obtained from the HPA database.

Correlation analysis of gene expression and immune infiltration

The correlations between CD2AP and MYH10 expression and immune cell infiltration in COAD were analysed via the Xiantao tool (<https://www.xiantaozi.com/products>). Correlation analysis was performed between CD2AP and MYH10 expression and the immune infiltration matrix data calculated via the ssGSEA algorithm. Additionally, the Xiantao tool was used to compare the differences in immune infiltration results between the high- and low-expression groups (based on the median expression) of the molecules, as calculated by the ssGSEA and ESTIMATE algorithms.

Screening small-molecule drugs

Differential genes between UC patients and normal samples in the merged dataset were analysed with a fold change greater than 2 and an adjusted *p* value (adjP) < 0.05. Further analysis focused on DEGs associated with MYH10 and CD2AP, which had correlation coefficients greater than 0.6 and *p* values < 0.05. Differential genes associated with MYH10 and CD2AP were uploaded to the CMap database (<https://clue.io/CMap>). Candidate small-molecule drugs were discovered through CMAP mode of action analysis. The enrichment score for each hypothetical drug ranged from −1 to 1. A negative enrichment score for a drug represents its reversal effect on the input DEGs, indicating its potential anti-UC activity on the UC-related gene set. Small-molecule compounds with a *p* value < 0.05 and an enrichment score < −0.6 were selected.

Molecular docking

To analyse the binding affinities and interaction modes between the drug candidate and its targets, the molecular docking software AutoDock Vina 1.2.2 was used. The molecular structure of the small-molecule drug was retrieved from PubChem Compound (<https://pubchem.ncbi.nlm.nih.gov/>). The 3D coordinates of CD2AP (PDB ID: 3U23; resolution: 1.11 Å) and MYH10 (PDB ID: 4pd3; resolution: 2.84 Å) were downloaded from the Protein Data Bank (PDB) (<http://www.rcsb.org/>). For the docking analysis, all protein and molecular files were converted into PDBQT format with water molecules excluded, and polar hydrogen atoms were added. Molecular docking studies were performed via AutoDock Vina 1.2.2 (<http://autodock.scripps.edu/>). The best-scoring docked conformation was selected and visualized via the PyMOL molecular graphics system (version 3.0.3 Open-Source).

Prognostic analysis of MYH10 and CD2AP expression in COAD

MYH10 and CD2AP expression levels were assessed for their potential prognostic utility in cancer using RNA sequencing data sourced from The Cancer Genome Atlas (TCGA) (<https://portal.gdc.cancer.gov/>). The Xiantao academic tool was employed to conduct statistical analysis.

Statistical analysis

The data are presented as the mean $\pm$ SD. The statistical significance was determined by unpaired Student's *t* test. All the statistical analyses were performed using R (version 4.3.1) and GraphPad Prism 9 (San Diego, CA). $P < 0.05$ was considered a statistically significant difference.

Data availability

The datasets analyzed during the current study are available in public databases such as TCGA (<https://portal.gdc.cancer.gov/>), GEO (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE87473>, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE38712>, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE75214>, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE92415>),

<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE87466>, <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE53306> and HPA (<https://www.proteinatlas.org/>). Further inquiries can be directed to the corresponding author.

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Author contributions

Chenhao Jiang, Teng Yue, Ziyao Jia and Lili Song: Writing—review & editing, Writing—original draft, Software, Methodology, Investigation, Conceptualization. Xiaohang Zeng and Ziyu Bao: Validation, Software, Investigation. Xinying Li: Writing—original draft, Supervision, Methodology. Zhuang Cui: Writing—review & editing, Supervision, Methodology. Qianqian Li and Wenyi Mi: Writing—review & editing, Resources, Project administration, Funding acquisition. All authors reviewed the manuscript.

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Declarations

Ethics approval and consent to participate

All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Tianjin Medical University. This study was conducted and reported in accordance with the ARRIVE guidelines to ensure transparency and reproducibility in animal research. All procedures were carried out in accordance with the relevant institutional guidelines and regulations. Informed consent was obtained from all subjects involved and the study with human samples was approved by the Ethics Committee of Jinghai Hospital, Tianjin, China. This study was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

Competing interests

The authors declare that they have no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to W.M. or Q.L.

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