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Identification of candidate biomarkers and pathways associated with vedolizumab response in T cell populations of IBD patients by WGCNA

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Abstract

Vedolizumab is a monoclonal IgG1 antibody that prevents T cells from migrating to the gut mucosa. The purpose of this study was to identify key genes with promising therapeutic targets, and molecular pathways associated with vedolizumab response. Gene expression profiles of the GSE234736 dataset were downloaded from the Gene Expression Omnibus (GEO). A co-expression network was constructed, and significant modules were identified using the weighted gene co-expression network analysis (WGCNA) package. Next, functional enrichment analysis was performed using the R package clusterProfiler to explore gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Then, protein-protein interaction (PPI) was constructed by using the function "exportNetworkToCytoscape" and visualized by Cytoscape software. There were three modules correlated with vedolizumab response: black (r=0.41; P<4e-05), magenta (r=0.3; P<0.004), and blue (cor = -0.29, P< 0.004). Genes in selected modules were mainly enriched in lymphocyte differentiation, cytoplasmic translation, and rRNA metabolic processes, respectively. KEGG pathway analysis showed that these genes were particularly enriched in Human T-cell leukemia virus 1 infection and protein processing in the endoplasmic reticulum. Furthermore, six selected hub genes were detected in each module by overlapping PPI and WGCNA networks. Finally, GO enrichment re-analysis of selected hub genes revealed 11 hub genes that were significantly enriched in the positive regulation of intracellular protein transport and regulation of alternative mRNA splicing. This study identified hub target genes and functional pathways that may provide new insights into responsiveness to vedolizumab, a targeted therapy for IBD.

Keywords: Vedolizumab, IBD, WGCNA, Gene ontology, Hub genes

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), also known as inflammatory bowel disease (IBD), are relapsing, chronic autoimmune disorders. IBD affects more than six million people worldwide and is considered a global emergency disease with a steadily increasing incidence and prevalence [1]. The pathogenesis of IBD is unknown, although it involves complex interactions among several factors, including environmental factors, genetic disposition, enteric microbiota, and immune responses [2, 3]. Growing evidence suggests that chronic inflammation associated with tissue injury is caused by the dysfunction of adaptive and innate immune pathways that play a critical role in the continuous inflammatory bowel response [4].

The currently available IBD therapies include a variety of untargeted and targeted therapies, with surgical intervention if required. Vedolizumab, a specific inhibitor of α4β7 integrin, has been approved for the treatment of UC and CD; however, its use is limited because of the occurrence of potentially serious adverse events [5]. In addition, despite an initial response to vedolizumab therapy, up to 35 % of IBD patients lose their response after 12 months [6]. Given that T-cells play a key role in regulating the inflammatory response associated with IBD, it has been suggested that vedolizumab inhibits the binding and subsequent trafficking of circulating T lymphocytes into the gut mucosa [7]. The underlying mechanism governing the T-cell migration in humans and the incidence of loss of response to vedolizumab therapy in IBD patients remains unclear.

During the last decade, weighted gene coexpression analysis (WGCNA) has been a systems biology tool based on pairwise associations between different variables used to construct gene networks and detect disease-associated key pathways [8]. The WGCNA workflow includes the construction of a gene co-expression network, identification of gene modules, relationship of modules to external information or clinical traits, studying inter-module relationships, and finding key drivers in interesting modules.

In the present study, WGCNA was performed based on RNAseq data of intestinal T cell populations of IBD patients to identify critical co-expression modules and key pathways associated with vedolizumab response, which may provide new insights into potential gene markers for understanding the responsiveness to vedolizumab therapy, as well as potential therapeutic targets for the treatment of IBD.

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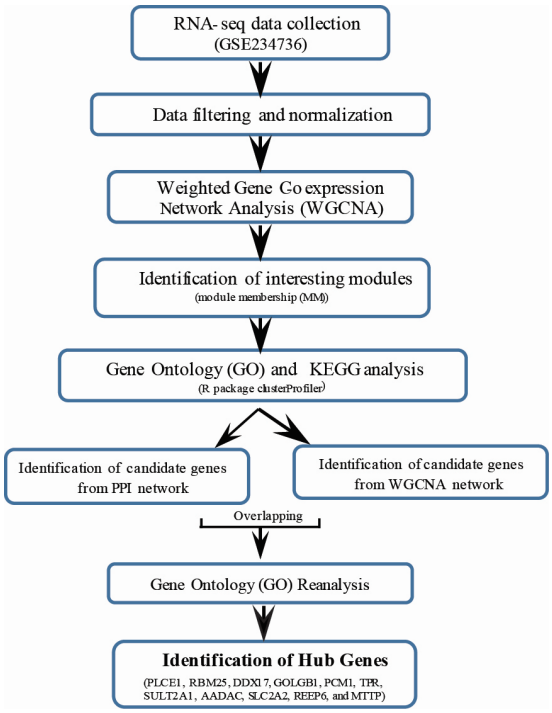

Fig. 1. The flow diagram of the study.

2. Material and methods

2.1. Data preparation and processing

The Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) was used to download the gene expression profile GSE234736 [9], including the associated clinical traits (tissue type, treatment, and treatment status). The gene expression levels of colon biopsies of 51 patients on vedolizumab at the time of sampling and 45 control patients were included in GSE234736. The "GSE234736_Supplementary_Table_2" file includes information on sex, age, tissue name, study group, inflammation status, days since the first dose of vedolizumab, vedolizumab treatment, vedolizumab response, αTNF treatment, and thiopurine treatment. The function "goodSamplesGenes" provided by the R package WGCNA was utilized to remove outlier samples. The counts were normalized using the variance-stabilizing normalization of the DESeq2 R package by removing all genes with counts < 15 in more than 75% of the samples. There were 11779 genes for further WGCNA analysis. Before proceeding, the "hclust" function was employed to detect sample outliers whose cut height surpassed 8e+04 and were thus excluded from the analysis. The workflow of this study is shown in Fig.1.

2.2. Network construction

The R Studio package WGCNA [8] was used to construct gene coexpression network and modules for the 11779 selected genes related to vedolizumab response. First, the soft thresholding power, β = 7, was used to compute the adjacency matrix and adjust the scale independence of the scale-free network. The adjacency matrix was then applied to calculate the topological overlap matrix (TOM), which quantifies the degree of resemblance of gene pairs with other genes in the network. Genes were then hierarchically clustered utilizing 1-TOM as the distance measure, and modules were identified in the resulting dendrogram by the cutreeDynamic algorithm with the following parameters: minimum module size = 30, deepSplit = 2. The other parameter settings were set to default.

2.3. Identification of clinically significant modules

The module eigengene (ME) was calculated for each module to describe the overall expression level of the genes in the module. Module membership (MM) was described as the intramodular connectivity between any gene and a particular module. Finally, module-trait associations were evaluated by calculating the correlations between MEs and clinical traits to identify significant associations.

2.4. Functional enrichment analysis of modules of interest

The enrichment analyses of GO and KEGG [10] were performed using the clusterProfiler v 4.10.1 package. Pathways with a p-value < 0.05 were considered statistically significant, and plot visualizations were performed using the ggplot2 package.

2.5. Module visualization and identification of hub genes

The PPI network of the genes in the significant modules was constructed using the function "exportNetworkToCytoscape". This function generates edge and node data files that can be imported using Cytoscape software (version 3.10.2, https://cytoscape.org) [11]. The Maximal Clique Centrality (MCC) algorithm in the CytoHubba plugin (version 0.1, https://apps.cytoscape.org/apps/cytohubba) was used to select candidate genes from the PPI network of each module. In addition, by using the criteria $|GS| \geq 0.2$ and $|MM| \geq 0.8$, a set of crucial genes was identified as predicted key genes. The common key genes between the PPI and WGCNA networks were selected as hub genes. After identifying hub genes, the R package clusterProfiler was applied to re-analyze GO enrichment for hub genes; P-value ≤0.05 and count ≥ 2 were considered significant.

3. Results

3.1. Construction of co-expression modules

After removing outliers, the top 11779 genes in 93 samples, including 50 IBD patients on vedolizumab treatment and 43 IBD control patients, were used to construct the co-expression network. The clinical traits of GSE234736 are shown in the sample-clustering dendrogram with a trait heatmap (Fig. 2). The network topology for soft-threshold powers ranging from 1 to 20 was calculated to select the best threshold. As shown in Fig. 3A, β = 7, which was the lowest power for which the scale-free topology fit index of > 0.93 was used as the soft threshold in this study. Then, by choosing 7 as a soft threshold, an adjacency matrix was constructed from a similarity matrix, and a topological overlap matrix (TOM) and corresponding dissimilarity (1-TOM) value were subsequently calculated. Finally, a dynamic tree-cut method was used to generate 24 modules, and 11 co-expression modules were identified after merging them with a correlation greater than 0.75. The gray module represents genes that were not assigned to any specific module and were not considered in the analysis (Fig. 3B). There were 1348, 3133, 2640, 598, 1033, 441, 884, 158, 355, 274, and 915 genes in the black, blue, cyan, darkgreen, darkturquoise, greenyellow, grey, grey60, magenta, tan, and yellow modules, respectively.

The interaction associations among the 11 modules

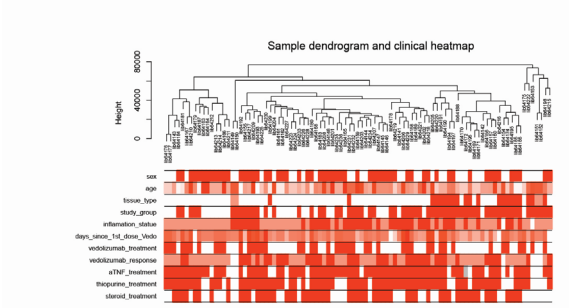

Fig. 2. Clustering dendrogram of 93 samples and clinical trait heatmap. Clustering was based on the processed expression data from GSE234736. The color intensity was proportional to sex (male, female), age, tissue type (colon, ileum, jejunum), study group, inflammation status (yes, no), days since the first dose vedolizumab, vedolizumab treatment (pre-treatment, on-treatment), vedolizumab response (responder, non-responder, and unknown), αTNF treatment (yes, no), thiopurine treatment (yes, no), and steroid treatment (yes, no).

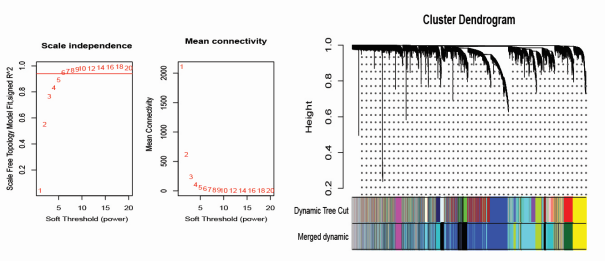

Fig. 3. (A) Analysis of scale-free index and average connectivity for various powers of soft threshold β. The x-axis indicates power, and the y-axis represents the scale-free fitting index and connectivity for each power. (B) Cluster dendrogram produced by average linkage hierarchical clustering of genes based on measurement of dissimilarity (1-TOM). Each branch on the graph indicates one gene, and each color band below represents a module that contains closely conserved genes. (C) Heatmap of the correlation between module eigengenes and the vedolizumab response. The black and magenta modules displayed a positive correlation with the response to vedolizumab, and the blue module was the most negatively correlated.

were calculated. The network heatmap of selected genes indicated the relative independence of different genes in different modules (Fig. 4A). In order to detect co-expression similarity between modules, eigengenes were clustered based on their correlation, and two main clusters were obtained (Fig. 4B). In addition, the eigengene adjacency heatmap revealed similar results (Fig. 4C).

3.2. Correlation between modules and vedolizumab response

By correlating module-sample eigengenes and clinical traits, the module-trait associations were analyzed to identify modules that were significantly associated with vedolizumab response. The results showed that the genes in the black module exhibited the highest positive correlation (r=0.41; P<4e-05), followed by magenta (r=0.3; P<0.004). In contrast, the blue module (cor = -0.29, P< 0.004) showed a significant negative correlation (Fig. 4D). Therefore, these three modules were ultimately selected as the key modules for vedolizumab response. Fig.5A, Fig.5B, and Fig.5C illustrate the relationship between the membership of the black, magenta, and blue modules and the GS, respectively.

3.3. Functional enrichment analysis of modules of interest

As the black, magenta, and blue modules were associated with the vedolizumab response, the genes in these modules were screened for further GO and KEGG analyses. For the biological process enrichment analysis, the results showed that the genes in the black module were mainly enriched in lymphocyte differentiation, leukocyte migration, T cell differentiation, and B cell activation (Fig. 6A), whereas for the magenta module (Fig. 6B), the genes were mainly related to cytoplasmic translation, Golgi vesicle transport, and RNA slicing, whereas for the blue module (Fig. 6C), the genes were mainly enriched in ribo-

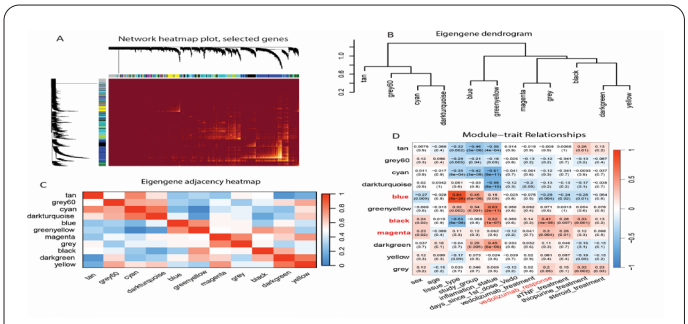

Fig. 4. Correlation between modules and significant module identification. (A) Heatmap of co-expression network modules. A single gene corresponds to each row and column of the heatmap. Different colors of the vertical and horizontal axes represent different modules. Higher adjacencies are indicated by a progressively darker red color, and low adjacencies between genes are indicated by a yellow color. (B) The eigengene dendrogram identified groups of correlated modules. (C) Heatmap plot of the adjacencies in the key gene network. Red represents positive correlation (high adjacency), while blue represents negative correlation (low adjacency). Squares of red color along the diagonal indicate the meta-modules. (D) Identification of significant modules associated with the vedolizumab response. The blue module was the most negatively correlated with response, and the black and magenta modules were the most positively correlated with response.

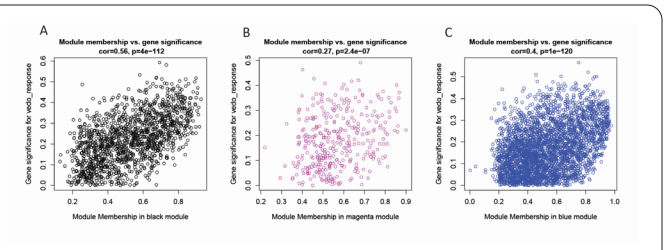

Fig. 5. Relationship between gene significance (GS) and module membership (MM) in the significant modules. MM was defined as the degree of association between a gene expression and each module, and GS indicates the correlation between an individual gene and vedolizumab response. GS & MM positively correlated refers to a strong association between the most significant genes in modules and the trait. (A) Relationship between the MM in the black module and GS for vedolizumab response. (B) Relationship between the MM in the magenta module and GS for vedolizumab response. (C) Relationship between the MM in the blue module and GS for vedolizumab response. Black, blue, and magenta modules had relatively high correlation coefficients (0.56, 0.4, and 0.27, respectively), and very low p-values (4e-112, 1e-120, and 2.4e-07, respectively) suggesting their potential role in responsiveness to vedolizumab in IBDs.

some biogenesis, rRNA metabolic process, and response to oxidative stress. Notably, black module genes were closely related to immune cell activation and differentiation.

KEGG enrichment results revealed that genes in the black module were mainly enriched in Human T-cell leukemia virus 1 infection, Epstein-Barr virus infection pathway, and protein processing in the endoplasmic reticulum (Fig.6D); genes in the magenta module were enriched in the ribosome pathway, protein processing in the endoplasmic reticulum, and nucleocytoplasmic transport (Fig. 6E); for the blue module, genes were enriched in protein processing in the endoplasmic reticulum, focal adhesion, and biosynthesis of nucleotide sugars (Fig. 6F).

3.4. Identification of key genes and network construction

Based on the criteria of $|GS| \geq 0.2$ and $|MM| \geq 0.8$, a set of 99, 16, and 296 genes were extracted from the black, magenta, and blue modules, respectively. Then, the PPI was constructed by the function "exportNetworkToCytoscape", which generates 1104, 203, and 2837 nodes and 121687, 1900, and 1349960 edges in black, magenta, and blue modules, respectively. The Maximal Clique Centrality (MCC) algorithm of the cytoHubba plugin of the Cytoscape software was applied to select the six potential key genes in each module. The overlapping of key genes in the PPI and WGCNA networks revealed hub genes CA12, FXYD3, PLCE1, SATB2, UGP2, and ZBTB7C in the black module (Fig. 7A). DDX17, GOLGB1, PCM1, PPIG, RBM25, and TPR were identified as hubs in the magenta module (Fig. 7B), whereas in the blue module there were 6 hub genes named AADAC, MTTP, REEP6, SLC28A1, SLC2A2, and SULT2A1 (Fig. 7C).

To understand the possible biological pathways of the selected hub genes, GO analysis was re-analyzed using the clusterProfiler package in R. Among the 18 hub genes, GO analysis revealed 11 selected hub genes that were enriched in several biological processes, including acylglycerol metabolic process, protein localization to the centrosome and microtubule organizing center, and regulation of alternative mRNA splicing via spliceosome (Fig. 7D). There were no statistically significant enriched GO terms for the MF and CC of the final hub genes. These results suggest that glycerolipid metabolism and alternative mRNA splicing play extremely important roles in the response to vedolizumab therapy and should be further investigated.

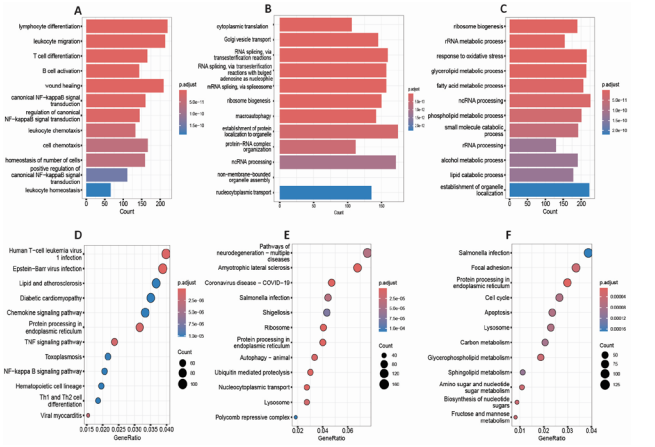

Fig. 6. Gene ontology and KEGG enrichment analysis of genes within the modules significantly associated with vedolizumab response. (A, B, and C) The top 12 GO terms of biological process analysis of black, magenta, and blue modules, respectively. The x-axis indicates the number of genes enriched in each term. The term color represents the degree of enrichment. Darker colors represent higher enrichment. (D, E, and F) Top 12 GO terms of KEGG analysis in black, magenta, and blue modules, respectively. The node size represents the gene count, and the node color represents the adjusted p-value of the term.

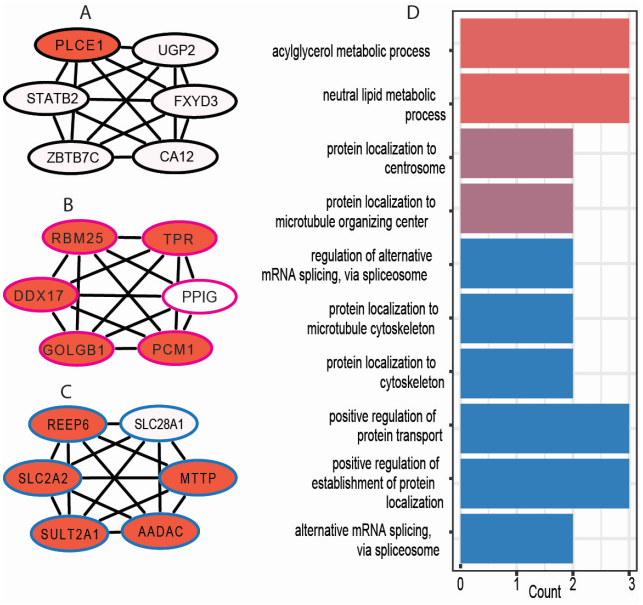

Fig. 7. Co-expression network of the hub genes in black (A), magenta (B), and blue (C) modules. Node red fill color shows the 11 selected hub genes. (D) Top 10 terms of biological process enrichment analysis of selected genes within the modules significantly associated with vedolizumab response. The x-axis shows the number of genes enriched in each term. The term color represents the degree of enrichment.

4. Discussion

Although the use of gut-selective monoclonal antibody drugs, including vedolizumab, an approved treatment for moderate to severe active IBD, the loss of response to vedolizumab therapy was reported to occur in up to 35% of patients [6]. In the present study, WGCNA analysis was performed to identify and predict the candidate pathways and genes associated with vedolizumab response. Among all recognized modules, the black, magenta, and blue modules were selected as the key modules of the study. Overlapping PPI and WGCNA networks identified candidate hub genes in the black, magenta, and blue modules.

Functional enrichment analysis showed no significant differences in gene interactions among the different modules, which was mainly linked to their shared functions. Enrichment analysis of the genes in the black module suggested their involvement in multiple GO pathways, including lymphocyte differentiation, leukocyte migration, wound healing, and NF-kB signal transduction, suggesting their potential role in regulating the progression of IBD. A previous study indicated that the NF-κβ signaling cascade acts as a central mediator in IBD inflammatory responses and malignancies, including gastrointestinal cancers [12]. Indeed, inactivation of NF-κβ impairs mesenchymal stem cell migration, adhesion, and leukocyte recruitment, suggesting that the NF-κB signaling pathway is an important regulator of inflammatory responses [13]. Additionally,

genes in the magenta and blue modules were significantly enriched in the pathways associated with mRNA processing and glycerolipid metabolism, respectively. Because mRNA splicing [14] and T-cell metabolism [15] play important roles in activated T cells during the maintenance of homeostasis, activation, and differentiation in autoimmune diseases such as IBD, genes in the magenta and blue modules may help us to further understand the molecular mechanisms associated with vedolizumab response and develop new therapeutic targets for IBD treatment.

KEGG pathway results revealed that the genes in the black module were enriched in the Epstein-Barr virus (EBV) infection pathway. EBV infection is most frequent in inflamed gastrointestinal mucosa and is found in 64% of ulcerative colitis and 55% of Crohn's disease patients [16]. A recent study demonstrated that IBD patients with positive EBV infection may manifest more severe immune disorders, including lympho-proliferative diseases, which are associated with the chronicity and poor prognosis of refractory IBD [17]. Genes in the magenta and blue modules were mainly enriched in ribosome and protein processing in the endoplasmic reticulum pathways. Tan et al. [18] reported that the regulation of endoplasmic reticulum stress on protein folding synthesis is the major factor influencing the integrity of the intestinal barrier and, if prolonged, may cause IBD through induction of the proinflammatory response [19].

In the present study, only hub genes associated with biological process GO terms were retained as selected hub genes. In total, there were 11 selected hub genes in modules of interest, including black (PLCE1), magenta (RBM25, DDX17, GOLGB1, PCM1, and TPR), and blue (SULT2A1, AADAC, SLC2A2, REEP6, and MTTP), which were mainly associated with the response to vedolizumab therapy. PLCE1 (phospholipase C epsilon 1) is an enzyme that catalyzes the hydrolysis of membrane glycerophospholipids and sphingolipids to generate various cellular mediators, that initiate intracellular cell growth, differentiation, and gene expression [20]. In addition to its role in the pathogenesis of multiple types of cancers through various pathways, a previous study showed that overexpression of PLCE1 can promote inflammation and stimulate the expression of multiple inflammatory cytokines via activation of the NF-κB signaling pathway [21]. Several studies have shown the implication of hub genes in the magenta module in mRNA splicing, protein synthesis, and transport. RBM25 (RNA Binding Motif Protein 25) and DDX17 (DEAD-Box Helicase 17) are essential regulators of transcription, splicing, and miRNA biogenesis in multiple human cell lines [22, 23]. Therefore, alternative splicing dysregulation may be a new mechanism contributing to the pathogenesis of Crohn's disease [24]. Growing evidence suggests that golgins, including GOLGB1 (Golgin B1), can tether transport vesicles and participate in membrane trafficking between the Golgi and other organelles, which has been suggested as a key contributor to innate immune signaling pathways [25]. Pericentriolar material 1 (PCM 1), which is present around centrioles, participates in several crucial cellular functions, including microtubule assembly. Interestingly, centrosome maturation is crucial for the secretion of a variety of soluble mediators, such as IL-6, IL-10, and CC-chemokine ligand 2, which activate interphase centrosome maturation in immune cells [26]. The protein encoded by the Translocated Promoter Region (TPR) gene plays several roles in the nucleus, including an increase in the total nuclear pore complex number in various cell types [27], and functions as an accessory protein that is critical for the three-prime repair exonuclease 2-dependent mRNA export pathway [28].

The hub genes in the blue module were mainly implicated in glycerolipid/ion metabolism and transport. Some scholars have pointed out that various infections and inflammatory conditions are associated with reduced levels of SULT2A1 (Sulfotransferase Family 2A Member 1), which may alter the metabolism and disposition of many xenobiotics in liver tissue [29]. Moreover, it has been suggested that MTTP (Microsomal triglyceride transfer protein) was downregulated by IBD-related proinflammatory cytokines [30] and was suggested as a potential drug target in colon and ileum IBD patients [31]. Arylacetamide deacetylase (AADAC), an enzyme primarily expressed in the liver and gastrointestinal tract, is involved not only in clinical drug degradation but also in triacylglycerol metabolism and pathogenesis, as its reduced expression is correlated with impaired triglyceride lipolysis, VLDL production and non-alcoholic fatty liver disease [32, 33]. A recent study showed that SLC2A2 (Solute Carrier Family 2 Member 2), an important glucose transporter, is highly correlated with tumor cell proliferation, and its methylation or decreased expression is positively associated with immune cell infiltration [34]. It has been suggested that REEP6 (Receptor Accessory Protein 6) can specifically interact with CXC motif chemokine receptor 1, leading to the activation of the IL-8/CXCR1 signaling pathway [35]. All the above suggestions are in agreement with what has been reported in GO terms of selected hub genes concerning the acylglycerol metabolic process, protein localization to the centrosome and to the microtubule organizing center, and regulation of alternative mRNA splicing.

Nevertheless, despite the relatively high number of samples in the GSE234736 dataset, the current study had some limitations. These findings need to be confirmed through laboratory in vivo and in vitro experiments. In addition, to confirm the reliability of these results, it is necessary to validate the findings using another confirmation dataset.

5. Conclusion

In summary, this study performed an integrated bioinformatics analysis to identify key genes and pathways associated with vedolizumab response, thereby improving our current knowledge of the pathogenesis of IBD. Moreover, these results may provide new insights for understanding the responsiveness to vedolizumab therapy and discovering new therapeutic targets for the treatment of IBD.

Abbreviations

AADAC: Arylacetamide Deacetylase; **CA12**: Carbonic Anhydrase 12; **CD** : Crohn's Disease; **DDX17**: DEAD-Box Helicase 17; **FXYD3**: FXYD Domain Containing Ion Transport Regulator 3; **GEO** : Gene Expression; Omnibus; **GO** : Gene Ontology; **GOLGB1**: Golgin B1; **GS** : Gene Significance; **IBD**: Inflammatory Bowel Disease; **KEGG** : Kyoto Encyclopedia of Genes and Genomes; **MCC** : Maximal Clique Centrality; **ME** : Module Eigengene; **MM** : Module Membership; **MTTP**: Microsomal Triglyceride Transfer Protein; **PCM1**: Pericentriolar Material 1; **PLCE1**: Phospholipase C Epsilon 1 ; **PPI** : Protein-Protein

Interaction ; **PPIG**: Peptidylprolyl Isomerase G; **RBM25**: RNA Binding Motif Protein 25; **REEP6**: Receptor Accessory Protein 6; **SATB2**: SATB Homeobox 2; **SLC28A1**: Solute Carrier Family 28 Member 1; **SLC2A2**: Solute Carrier Family 2 Member 2; **SULT2A1**: Sulfotransferase Family 2A Member 1; **TOM** : Topological Overlap Matrix; **TPR**: Translocated Promoter Region Nuclear Basket Protein; **UC**: Ulcerative Colitis; **UGP2**: UDP-Glucose; Pyrophosphorylase 2; **WGCNA** : Weighted Gene Co-expression Network Analysis; **ZBTB7C**: Zinc Finger And BTB Domain Containing 7C.

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Not applicable.

Conflict of interests
The author declares that he has no conflicts of interest.

Consent for publications
The manuscript has been read and approved by the author.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed consent
The authors declare that no patients were used in this study.

Availability of data and material
The author has to declare that he embedded all data in the manuscript. All the data for this study were obtained from the publicly available GEO database, https://www.ncbi.nlm.nih.gov/geo

Author contributions
Abdelk ader Oumeddour designed the study, acquired, analyzed, and interpreted the data, performed the statistical analysis, drafted the manuscript, and commented on previous versions of the manuscript. The author has read and approved the final manuscript.

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