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ORIGINAL ARTICLE

Analysis of key genes and micro-RNA-mRNA regulatory networks in women with ulcerative interstitial cystitis/pain bladder syndrome

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Abstract

Introduction and hypothesis This aim of this study was to better understand ulcerative interstitial cystitis/painful bladder syndrome (IC/PBS) at the molecular level and provide new clues related to diagnosis and treatment.

Methods The microarray data set GSE11783, including the mRNA and miRNA profiles of bladder tissue obtained at cystoscopic biopsy from patients with ulcerative IC/PBS (presence of at least one Hunner's ulcer) and normal controls, was downloaded from the GEO (Gene Expression Omnibus) database (National Center for Biotechnology Information). These were evaluated using Greenspring GX and Ingenuity Pathway Analysis (IPA) software. The differentially expressed genes (DEGs) and miRNAs (DEMs) in these two groups were identified. Subsequently, the DEGs were subjected to functional analysis, and a protein-protein interaction (PPI) network was constructed. Finally, the miRNA-mRNA regulatory network was visualized using Cystoscope software.

Results Four DEMs and 1521 DEGs were identified between the ulcerative IC/PBS and control groups. The PPI network of the DEGs was constructed by STRING, which was composed of 393 nodes and 1039 edges, including 221 upregulated genes and 172 downregulated genes. Moreover, 27 genes in the PPI network were identified as hub genes in the IC/PBS group, e.g., PNOC, SSTR1, FPR3, GPR18 and APLNR. Subsequently, 27 clusters were selected from the PPI network using MCODE. It was shown that the most significant cluster consisted of 22 nodes and 231 edges. Moreover, miR-21 was the most significantly upregulated miRNA and was predicted to target one upregulated gene (RASGRP1) and two downregulated genes (KLF5 and SC5D).

Conclusions The results of this data mining and integration provide further information on the possible molecular basis of IC/PBS pathogenesis as well as potential biomarkers and therapeutic targets for ulcerative IC/PBS diagnosis and treatment.

Keywords Bioinformatics analysis · Interstitial cystitis/painful bladder syndrome · Microarray expression profiles · miRNA-mRNA interaction

Introduction

Interstitial cystitis, or painful bladder syndrome (IC/PBS), is a chronic bladder disorder that has a combination of symptoms, including lower abdominal pain, urinary urgency, and urinary frequency [1]. It can develop in people at any age, though the symptoms may vary within age groups [2]. According to published literature, the prevalence of IC/PBS is 45 cases per 100,000 women and 8 cases per 100,000 men [3]. Based on cystoscopy examinations, IC/PBS can be separated into two subtypes: classic Hunner's ulcerative and nonulcerative disease [4]. When classic IC/PBS patients' biopsies were analyzed, the histological results showed mucosal ulceration and extensive inflammation [5]. The etiology of IC/PBS is still not understood thoroughly, though there are several postulated mechanisms that researchers have raised before (mast cell activation with inflammation, toxic substances absorption, mucus layer with deficient

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Shengzhuo Liu and Shijian Feng contributed equally to this work.

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glycosaminoglycan, chronic inflammatory reaction in subepithelial bladder layers, etc.).

According to the American Urological Association (AUA)'s National Urology Research Agenda in 2010, IC/PBS is one of the urological disorders that needs to be investigated further through basic to clinical research, especially for diagnosis and biomarkers [6]. However, there is no gold standard for IC/PBS diagnosis. The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) raised a set of inclusion and exclusion criteria for the diagnosis of IC/PBS, and 40% of all IC/PBS patients could be diagnosed based on these criteria [7]. IC/PBS, based on current diagnostic criteria, still represents a spectrum of disorders, which makes it difficult to develop a highly sensitive universal diagnostic tool for IC/PBS and effective therapy. There is no precise molecular marker for IC/PBS diagnosis; clinicians have to rule out several symptoms common to these comorbid diseases and then begin the treatment for IC/PBS [8, 9]. Recent literature reveals several biomarkers for diagnosis, including heparin-binding EGF-like growth factor (HB-EGF), antiproliferative factor (APF), platelet-derived endothelial cell growth factor (PD-ECGF), and vascular endothelial growth factor (VEGF). However, none of these biomarkers are highly reliable for diagnosing the disease.

Microarray technology has been applied to the investigation of genetic aberrations involved in diseases. This technology allows us to better understand the molecular characterization of IC/PBS through direct examination of the gene expression of bladder biopsies. One previous study with microarray analysis data investigated the gene expression differences between IC/PBS patients (NIDDK criteria) and asymptomatic controls [10]. Nevertheless, there is no study to date that integrates these microarray data sets to identify key genes and elucidate miRNA-mRNA regulatory networks in IC/PBS and controls.

Bioinformatics has become an important part of many areas of biology, and it combines biology, computer science, mathematics, and statistics to analyze and interpret biological data. The present study screened the differentially expressed miRNAs (DEMs) and genes (DEGs) in ulcerative IC/PBS bladder biopsy tissues and healthy control bladder biopsy tissues using microarray analysis. The gene expression arrays were obtained from the GEO (Gene Expression Omnibus) database, which archives and freely distributes microarray next-generation sequencing and other forms of high-throughput functional genomics data submitted by researchers. Moreover, functional enrichment analysis and protein-protein interaction (PPI) analysis were performed for DEGs. Furthermore, a regulatory network was constructed, and functional analysis of miRNA-targeted genes was also performed. The results of the data mining and integration helped reveal the molecular basis of IC/PBS pathogenesis as well as potential biomarkers and therapeutic targets for IC/PBS diagnosis and treatment.

Methods

Study group

The data set [11] included 11 samples, 5 IC/PBS samples and 6 control samples. The genetic analysis of the whole cohort of IC/PBS bladder biopsies available for this study likely would have yielded conflicting results; therefore, we restricted the index analysis in our study to women with IC/PBS who had classical IC/PBS symptoms and had a Hunner's ulcer found by cystoscopy. All the patients were females. The mean age of the IC/PBS patients was 78.0 ± 7.5, whereas the mean age of the healthy controls was 59.2 ± 13.2 ($p = 0.052$). The mean VAS (visual analog score) of the IC/PBS patients was 69.4 ± 9.4, whereas the mean VAS score of the healthy controls was 19 ± 26 ($p = 0.016$). The mean duration of symptoms in IC/PBS patients was 32.6 ± 23.6 months, whereas the mean duration of symptoms of the healthy controls was 7.7 ± 10.8 months ($p = 0.143$) (Supplementary Table 1). This study was approved by the ethics committee of the West China Hospital of Sichuan University, China, and was in compliance with the Helsinki Declaration.

Microarray data

The gene expression profiles (GSE11783) of the ulcerative IC/PBS samples were downloaded from GEO (http://www.ncbi.nlm.nih.gov/geo). The GEO database is a functional genomics data repository that is accessible to the public, and it is used to store microarray and sequencing data. All the IC/PBS patients with Hunner's ulcer in the GEO database were evaluated according to the NIDDK criteria, whereas the control group did not show these cystoscopic findings. Three to four cold-cup biopsies (20 mm^3 in size) from bladder tissue, excluding the trigone, were collected.

Data processing

Normalization and subsequent data processing were performed using GeneSpring GX v11.5 software. The DEGs showing statistical significance between the two groups were identified. Reverse transcription-polymerase chain reaction (RT-PCR) was performed to verify the differences identified by the microarray analysis. The false-positive results of the microarray were then corrected by calculating the adjusted p value (adjusted p value) using

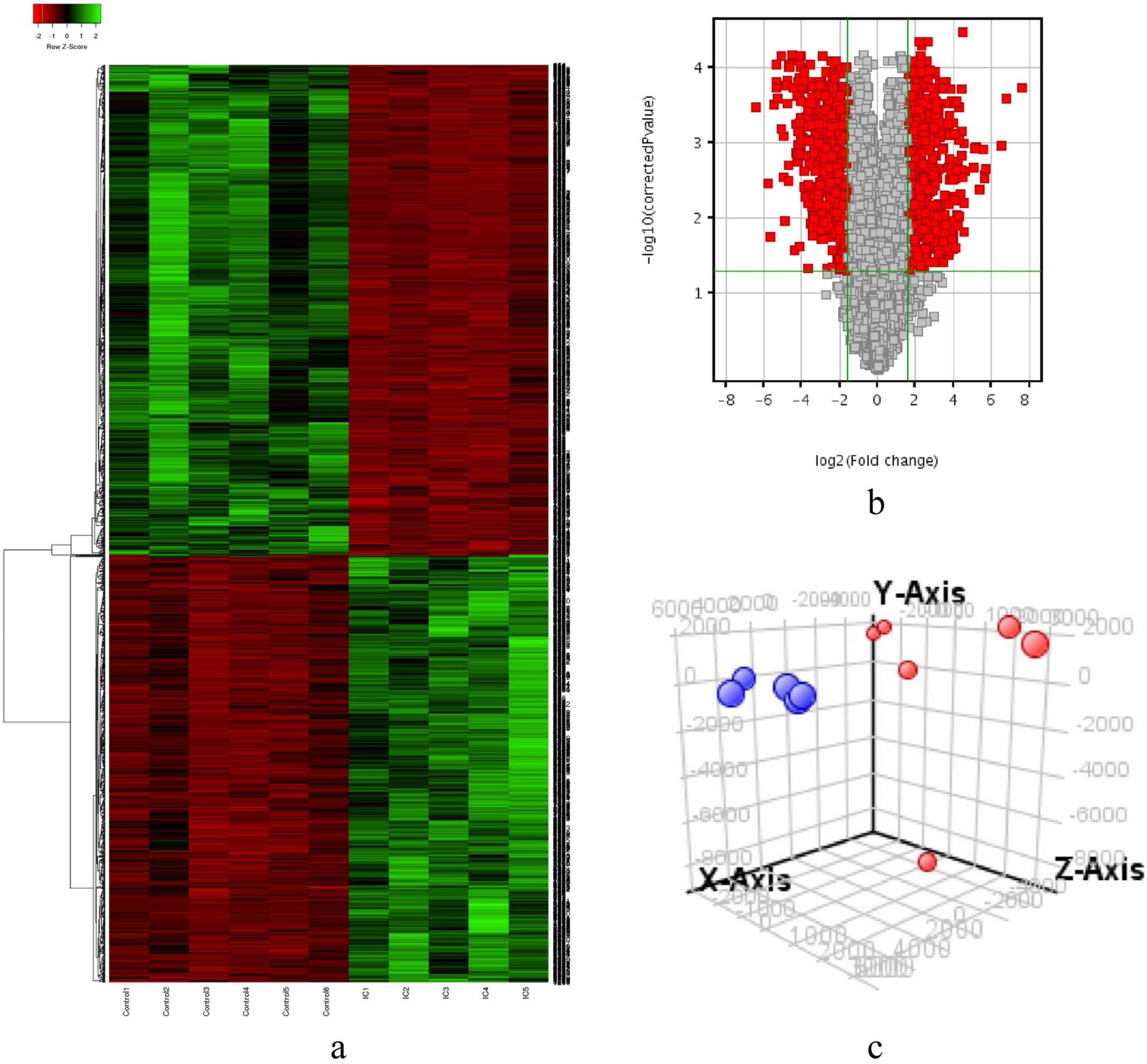

Fig. 1 **a** Heat map of the significant differently expressed mRNAs and miRNAs in interstitial cystitis (red: upregulated; green: downregulated); **b** volcano plot of upregulated genes and downregulated genes; **c** heterogeneity test of the included samples (red: interstitial cystitis samples; blue: control samples)

the Benjamini-Hochberg method. The cutoff criteria were adjusted p value < 0.001 and |logFC| > 3.0.

Gene ontology (GO) and pathway analysis

FUNRICH is a web resource that offers the functional interpretation of a large number of genes derived from genomic studies (http://www.funrich.org/). In the present study, FUNRICH was used to perform gene ontology (GO) analysis. The ontology contains three hierarchies: biological process, cellular component, and molecular function. The p value denoted the significance of the GO and pathway term enrichment in the DEGs. The cutoff criterion was $p < 0.05$.

Ingenuity Pathway Analysis (IPA) software was used to analyze the signaling pathways, upstream regulators, diseases, and disorders specific to ulcerative IC/PBS by comparing the microarray-generated transcriptomes of ulcerative IC/PBS bladder biopsy tissue and control bladder tissue. DEGs, which were detected by GeneSpring, were uploaded to IPA using the core analysis option to determine which signaling pathways were regulated in ulcerative IC/PBS bladder tissues.

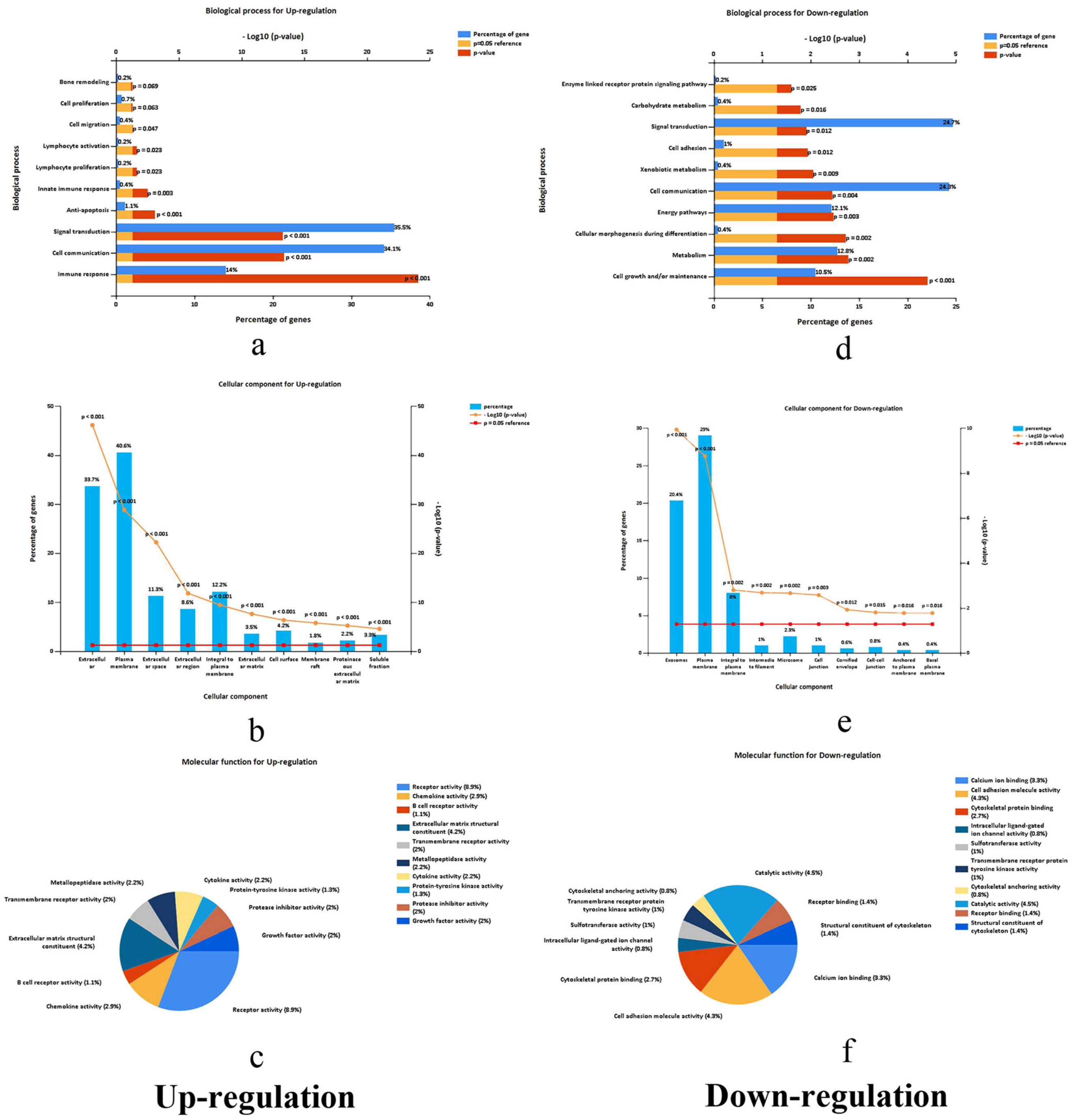

Fig. 2 Enriched GO terms for the upregulated genes: **a** biological process (BP); **b** cellular component (CC); **c** molecular function (MF). Enriched GO terms for the downregulated genes: **d** biological process (BP); **e** cellular component (CC); **f** molecular function (MF)

Establishment of a protein-protein interaction (PPI) network and cluster selection

In the present study, the PPI network of DEGs was constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins software (STRING, http://string.embl.de/). STRING is a biological database of known and predicted PPIs, which can provide a system-wide view of cellular processes. The data are integrated and weighted, and a confidence score is calculated for all protein-protein interactions. The cutoff criterion was confidence score ≥ 0.9. To find clusters of genes in the PPI network, molecular complex detection (MCODE) was then applied. The cutoff criteria were “degree cutoff = 2,” “node score cutoff = 0.2,” “k-core = 2,” and “maximum depth = 100.”

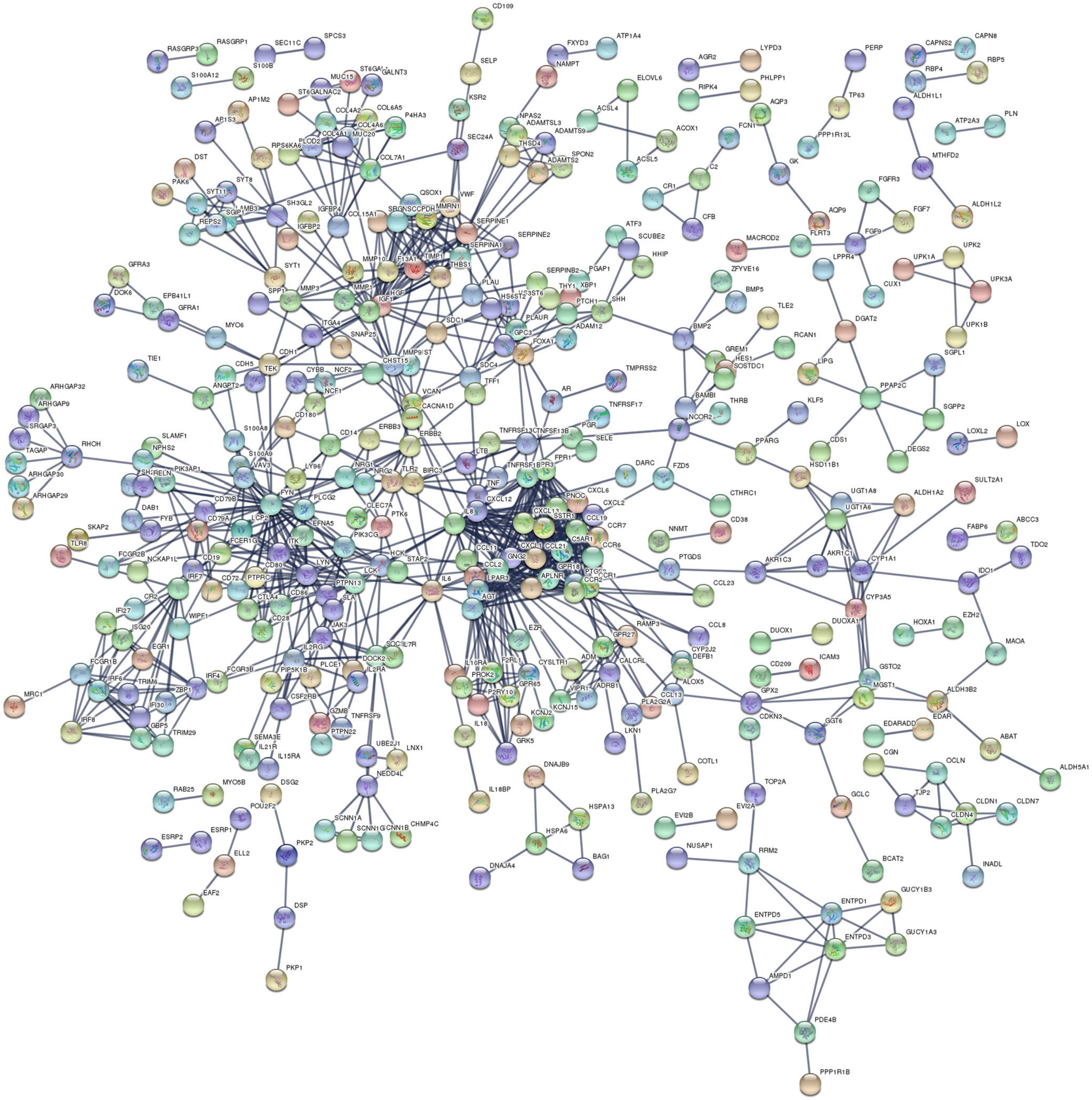

Fig. 3 Protein-protein interaction network of differentially expressed genes. (Network nodes represent proteins; colored nodes: query proteins and first shell of interactors; white nodes: second shell of interactors; empty nodes: proteins of unknown 3D structure; filled nodes: 3D structure is known or predicted; edge: protein-protein associations)

miRNA-mRNA regulatory network

The target genes of DEMs were predicted using TargetScan (http://www.targetscan.org/), which is an online program that predicts targets of miRNAs by seeking the specific sequence complementary to the seed region of each miRNA. Predicted targets are ranked according to the predicted efficacy of targeting as calculated using the cumulative weighted context ++ scores of the sites. In the present study, the top 100 genes were selected as the target genes of each miRNA. Subsequently, miRNA-mRNA regulatory networks, which depicted interactions between miRNAs and their potential targets in human bladder smooth muscle cell response to mechanical stretch, were visualized using Cytoscape version 3.6.0.

Results

Identification of DEGs and DEMs

After normalization by the RMA algorithm and SAM analysis of raw data, 1521 significant DEGs (758 upregulated genes and 763 downregulated genes) and 4 DEMs were identified between the ulcerative IC/PBS and control groups. In addition, the expression levels of these miRNAs and mRNAs were presented using heat maps. The heterogeneity test of each sample is shown in Fig. 1.

Functional enrichment analysis

GO analysis demonstrated that the most significantly enriched GO terms that corresponded to upregulated genes were “immune response” (ontology: BP), “extracellular” (ontology: CC), and “receptor activity” (ontology: MF), whereas the most significantly enriched GO terms that corresponded to downregulated genes were “cell growth and/or maintenance” (ontology: BP), “exosomes” (ontology: CC), and “calcium ion binding” (ontology: MF) (Fig. 2).

Furthermore, IPA showed that the top canonical pathways that corresponded to upregulated genes were “granulocyte adhesion and diapedesis,” “altered T cell and B cell signaling in rheumatoid arthritis,” “agranulocyte adhesion and diapedesis,” “primary immunodeficiency signaling,” and “communication between innate and adaptive immune cells,” whereas the most significantly enriched pathways that corresponded to downregulated genes were “LPS/IL-1 mediated inhibition of RXR function,” “xenobiotic metabolism signaling,” “superpathway of melatonin degradation,” “serotonin degradation,” and “melatonin degradation I” (Supplementary Table 2). The top upstream regulators of upregulated genes were lipopolysaccharide, IFNG, TNF, IL10, and IL4, while CBX5, beta-estradiol, ESR2, ZEB1, and WISP2 were the top upstream regulators of downregulated genes (Supplementary Table 3). The top disease and disorders associated with the upregulated genes were “inflammatory response,” “immunological disease,” “connective tissue disorders,” “inflammatory disease,” and “organismal injury and abnormalities,” whereas the top disease and disorders associated with the downregulated genes were “cancer,” “organismal injury and abnormalities,” “dermatological diseases and conditions,” “gastrointestinal disease,” and “reproductive system disease” (Supplementary Table 4).

Establishment of the PPI network and identification of hub genes

The PPI network of DEGs was constructed by STRING and was composed of 393 nodes and 1039 edges, including 221 upregulated genes and 172 downregulated genes (Fig. 3). In addition, when the interaction scores were applied and sorted from highest to lowest, the top interactions in the PPI network were identified, e.g., the TNFRSF1B, TNF, SYT1, SNAP25, SERPINE1, and PLAUR genes. When “degrees ≥ 20” was set

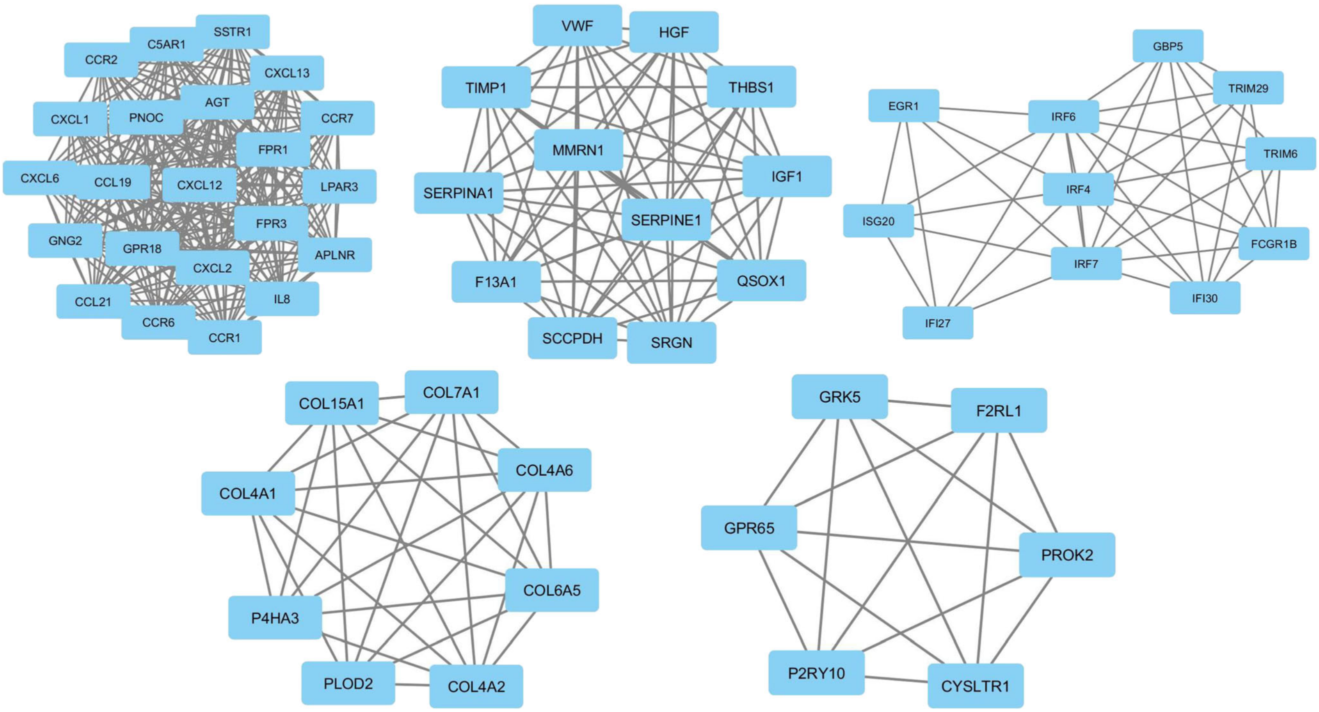

Fig. 4 Top five significant modules/clusters from the protein-protein interaction network. (Network nodes represent proteins; edge: protein-protein associations)

as the cutoff criterion, 27 genes in the PPI network were identified as hub genes in IC/PBS, e.g., PNOC, SSTR1, FPR3, GPR18, APLNR, AGT, CCR6, CXCL6, LPAR3, FPR1, C5AR1, and GNG2. Subsequently, 27 clusters were selected from the PPI network using MCODE, and it was shown that the most significant cluster consisted of 22 nodes and 231 edges. In addition, the MCODE analysis showed that each cluster contained one “seed” gene, for example, CCL21, SERPINA1, TRIM6, PLOD2, and P2RY10 were identified as the “seed” genes in their own clusters (Fig. 4).

Construction of the microRNA-target regulatory network

The target genes of four miRNAs were predicted by TargetScan. In our study, miR-21 was the most significantly upregulated miRNA and was predicted to target one upregulated gene (RASGRP1) and two downregulated genes (KLF5 and SC5D). MiR-4435-2HG was another upregulated miRNA and was predicted to target AQP1 and TNFRSF13C, which were upregulated genes. MiR-155HG was upregulated and predicted to target three upregulated genes, namely, FGF7, TDO2, and ZNF385D, and four downregulated genes, namely, AKR1C1, WEE1, WWC1, VAV3, and CHST9. MiR-205HG was the only downregulated miRNA and was predicted to target three downregulated genes, including SCNN1A, DST, and FUT9, and one upregulated gene (CALCRL) (Fig. 5).

Discussion

Currently, to confirm the diagnosis of IC/PBS, clinicians must go through differential diagnosis based on the symptoms and then obtain bladder biopsies to confirm the histological characteristics of IC/PBS. However, there is no standardized biopsy procedure for such biopsies to date. In addition, in some cases, the cystoscopic findings, urine markers, or patient symptoms do not correlate well with histological findings of the obtained data and cannot be compared in a systematic manner [12, 13]. Based on the difficulties in clinical practice, clinicians need a fast and valid alternative method to detect IC/PBS and thereby to start the treatment in advance. Moreover, the pathophysiology and etiology of IC/PBS are still unclear. Therefore, it is important to explore the molecular differences between IC/PBS and control bladders, which might be useful in guiding future investigations regarding diagnosis and pathophysiology.

In the present study, 521 significant DEGs, including 758 upregulated genes and 763 downregulated genes, and 4 DEMs were identified between the ulcerative IC/PBS group and the control group. Among the DEGs, the top five interaction scores in the PPI network were identified, namely, TNFRSF1B, TNF, SYT1, and SNAP25. Twenty-seven genes in the PPI network were identified as hub genes in IC/PBS, namely, PNOC, SSTR1, FPR3, and GPR18. Subsequently, 27 clusters were selected from the PPI network using MCODE, and CCL21, SERPINA1, TRIM6, PLOD2, and P2RY10 were identified as the “seed” genes.

PNOC encodes a preproprotein, which regulates multiple protein products. These products include nociceptin, nocistatin, and orphanin FQ2 (OFQ2). Nociceptin is a 17-amino-acid peptide and is a natural ligand for the orphan G protein-coupled receptor (GPCR) Opioid Receptor Like-1 (ORL1) that is also known as NOP, OP4, or LC132 [14]. Both nociceptin and the ORL1 receptors (NOP) have a high degree of sequence similarity to dynorphin and the kappa opioid receptor. A previous study showed that N/OFQ was

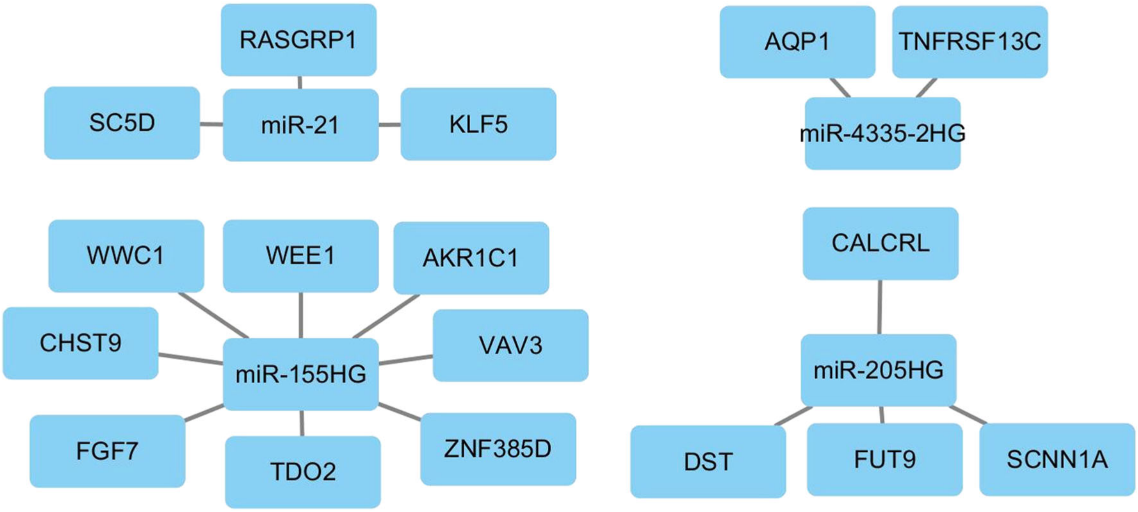

Fig. 5 MicroRNA-mRNA regulatory networks in interstitial cystitis. Upregulated microRNAs such as miR-21, miR-4435-2HG, and miR-155HG and downregulated miR-205HG were identified as key microRNAs in IC/PBS

involved in pain perception [15]. The most recently published literature regarding PNOC was conducted by Wachman et al., and they found that the PNOC genotype was correlated with neonatal abstinence syndrome outcomes [16]. Some researchers also noticed that PNOC might be involved in impaired emotional and behavioral control [17]. This evidence indicated that PNOC might be involved in pain, emotions, and some other syndromes in IC/PBS patients. SSTR1 is somatostatin receptor type 1 and has two active forms (14 and 28 amino acids). It regulates cell proliferation and may be a regulator of cell growth and development. The biological effects of somatostatins are controlled by a family of G protein receptors [18]. The FPR3 gene encodes a 351-amino-acid peptide that shares 69% identity with FPR and 83% identity with FPR2, which is also known as FPRL1 [19, 20]. The chemoattractants and N-formylmethionyl-leucyl-phenylalanine, which bind to the FPR, induce leukocyte recruitment at the sites of inflammation. This evidence suggested that the IC pathophysiological process involves the immune system, which supports previous theories.

MiRNAs, first discovered in *Caenorhabditis elegans*, are found in most eukaryotes [21]. It is also predicted that approximately 30% of protein-coding genes are regulated by miRNAs in humans [22, 23]. To better understand the correlation between the gene expression and miRNA as well as their target genes in IC/PBS, we constructed the miRNA-target regulatory network. Our study showed that miR-21 was the most significantly upregulated miRNA and was predicted to target one upregulated gene (RASGRP1) and two downregulated genes (KLF5 and SC5D). MiRNA-21 is an abundantly expressed miRNA in multiple cell types. Upregulation of this miRNA is associated with many cancers [24, 25]. Recent functional studies found that miRNA-21 regulates cell growth, migration, and invasion [26, 27]. MiR-205HG was the only downregulated miRNA, and it is an epithelial-specific miRNA involved in the epithelial-mesenchymal transition and differentiation fate of stem cells in mammary glands. It participates in tumor occurrence, development, and prognosis of several tumors [28–30].

There are several limitations to our study. First, the lack of experimental validation is a reasonable limitation. The predicted results obtained from bioinformatics analysis could be verified by further experimental research in the future. Second, this study has narrowed down the search for IC/PBS gene markers, and the next research step would be to run similar tests (identified as useful in the Hunner's ulcer group) in a larger group of women with a diagnosis of IC/PBS based on symptoms and glomerulations with petechial hemorrhages on empty and refill cystoscopy. The present study is a pilot study to facilitate future research, and the findings of this pilot study comparing a small group of women with IC/PBS and Hunner's ulcers to healthy controls will also help facilitate a power analysis to determine the number of samples required for a future study and to apply these genetic tests to a larger group of women with IC/PBS. Third, the small sample of gene expression could induce bias in the bioinformatics analysis. However, the findings are positive and will enable the identification of gene markers present in the Hunner's ulcer group when testing a larger cohort. The markers currently identified may be useful guides for further research to develop a diagnostic tool and more effective therapies for a broader group of women with IC/PBS.

Conclusions

The present study identified PNOC, SSTR1, and FPR3 as key genes. Upregulated microRNAs such as miR-21, miR-4435-2HG, and miR-155HG and downregulated miR-205HG were identified as key microRNAs in IC/PBS. The results suggest that PNOC might be involved in the pain syndrome of IC/PBS, whereas FPR3 could modulate inflammation in IC/PBS pathology. The results of this data mining and integration help reveal the molecular basis of ulcerative IC/PBS pathogenesis as well as potential biomarkers and therapeutic targets for ulcerative IC/PBS diagnosis and treatment.

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Compliance with ethical standards

Conflicts of interest None.

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