Multi-omics enables IC/BPS mechanism exploration

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ABSTRACT

Interstitial cystitis/bladder pain syndrome (IC/BPS), characterized by intense pelvic pain and urinary symptoms, is a severely debilitating and chronic disorder. The incidence of IC ranges from 0.01% to 6.5% with about five times more diagnosed females than the males. The etiology and pathophysiology of IC still remain an enigma, which makes the diagnosis difficult and treatment challenging. There are great chances of misdiagnosis or underdiagnosis, and it usually takes 2-11 years to get an accurate diagnosis. The current therapies of IC showed limited effects and relatively high recurrence rates in the long-term follow-up. About 10% of the diagnosed patients have to receive destructive surgeries (augmentation ileocystoplasty, urinary diversion, etc.) followed by stepwise therapeutic approaches, and 20% of whom have to face the failures. Therefore, there is a pressing need to understand the molecular mechanisms underlying the IC development and to identify more efficient targets for therapeutic treatments. Among the proposed mechanisms, barrier dysfunction was the most important one. However, more and more evidence proved that IC/BPS may involve multiple systems and its symptoms are primarily presented in the bladder, resulting barrier dysfunction. Therefore, systematic multi-omics studies can provide valuable insights into the pathophysiological mechanisms of IC/BPS.

METHODS

After obtaining IRB approval and informed consent, baseline information, stool, urine, blood, and bladder tissues were collected for downstream analysis. Changes in gut microbial communities, systemic metabolism, and bladder transcriptomics were detected and investigated to determine their relationships. The proposed mechanism was then validated through in vivo studies.

Methods

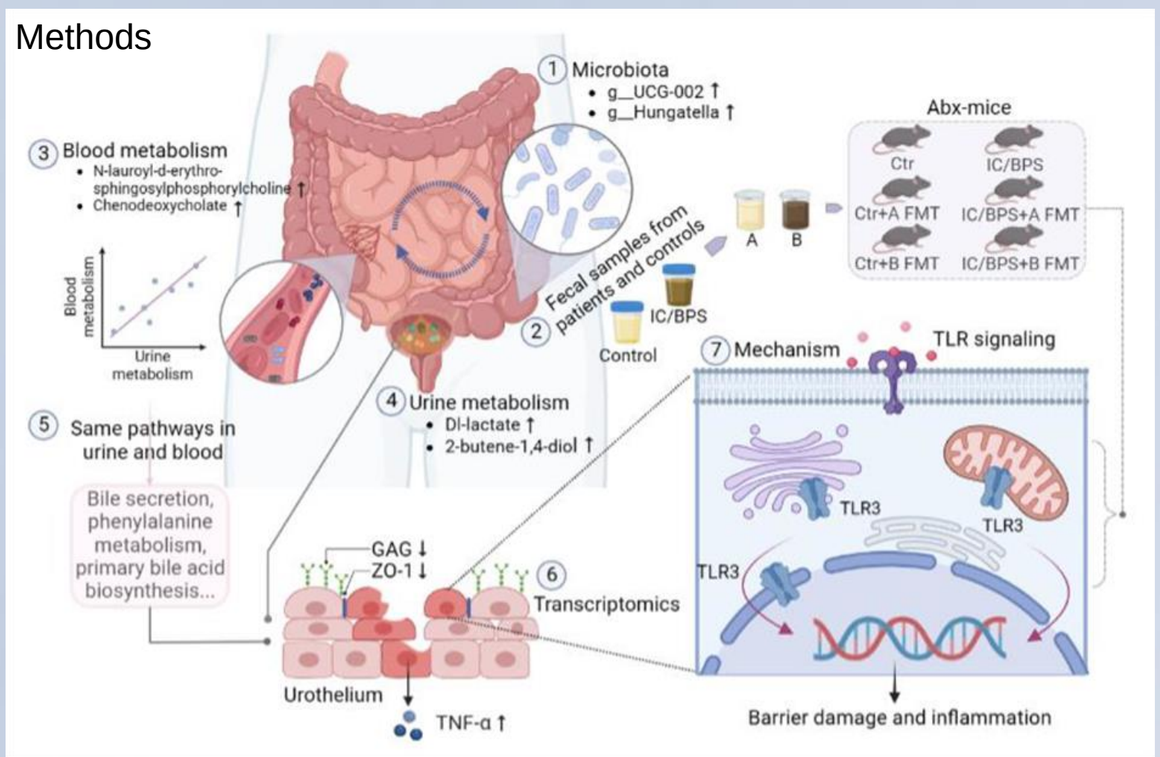


Fig. 1 LEfSe analysis on genus level (LDA>3 and P<0.05)

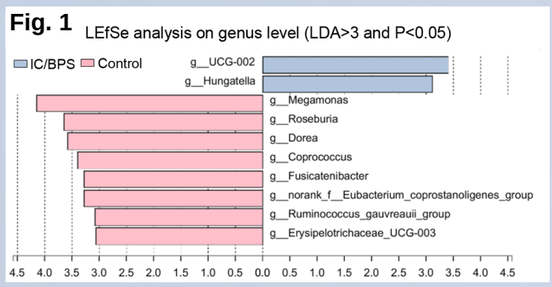
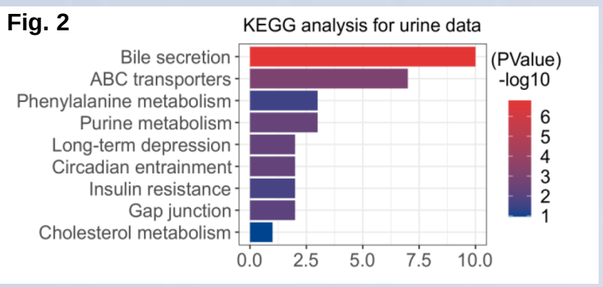


Fig. 2 KEGG analysis for urine data



RESULTS

The study found that IC/BPS patients had lower abundance of gut microorganisms, with UCG-002 and Hungatella as the dominant genera, and Megamonas and Roseburia as probiotic bacteria, based on 16S sequencing of gut microorganisms. Untargeted metabolomics analysis revealed that the differential metabolites in the blood of IC/BPS patients were mainly lipids and lipid-like molecules (34.75%), enriched in bile secretion and protein digestion and absorption pathways, while differential metabolites in the urine were mainly organic acids and their derivatives (27.6%), enriched in bile secretion and ABC transport pathways. Transcriptomics analysis showed that differentially expressed genes in IC/BPS bladder tissue were mainly involved in immune-related biological functions, barrier disruption signaling pathways, and inflammatory signaling pathways. Significant correlations were found between these three groups. Finally, the study validated the TLR3-mediated epithelial damage mechanism using western blot and qRT-PCR.

Fig. 3

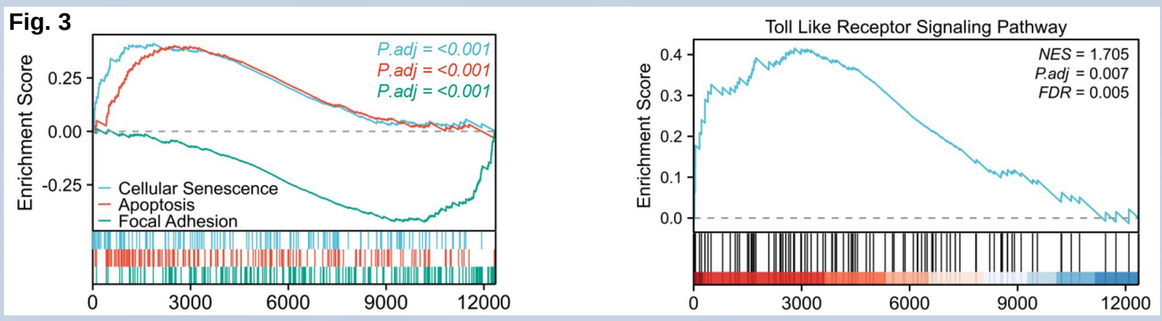
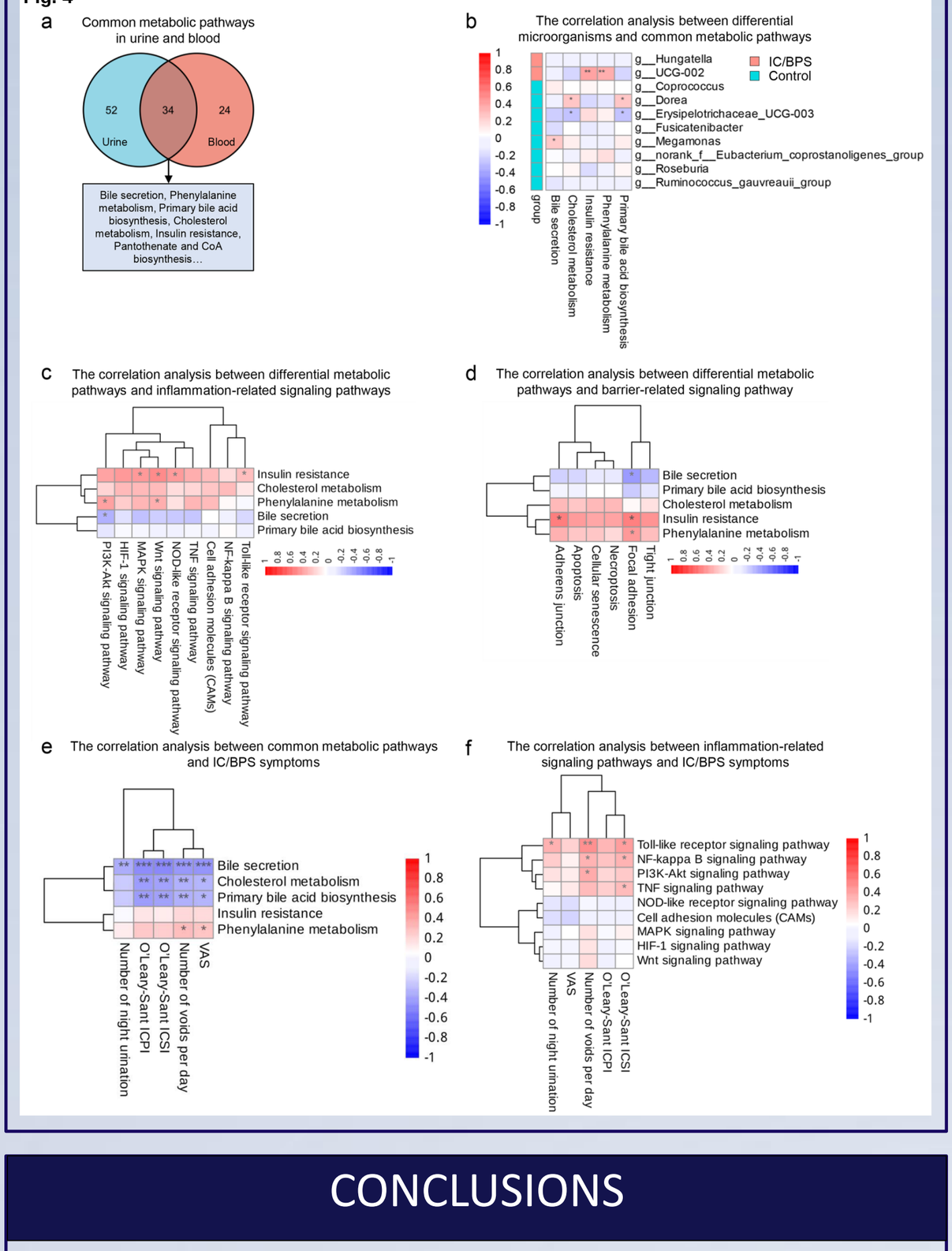


Fig. 4



CONCLUSIONS

Multi-omics revealed a TLR3-mediated epithelial damage mechanism in IC/BPS, and more studies were needed to verify these results.

REFERENCES

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2. Peng L, Li BY, Wang W, Gao XS, Zeng X, Luo DY. Identification of key genes in human urothelial cells corresponding to interstitial cystitis/bladder pain syndrome in a lipopolysaccharide-induced cystitis model. Neurourol Urodyn. 2021 Sep;40(7):1720-1729.