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VIRAL PATHOGENESIS

Alterations of the gut commensal *Akkermansia muciniphila* in patients with COVID-19

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ABSTRACT

Dysbiosis of gut microbiota is well established in coronavirus disease 2019 (COVID-19). While studies have attempted to establish a link between the gut commensal *Akkermansia muciniphila* (*A. muciniphila*) and COVID-19, the findings have been inconsistent and sometimes controversial. The intestinal microbial abundance information of COVID-19 patients was acquired and analysed from GMrepo database. Subsequently, *A. muciniphila's* metabolites, target-genes, and metabolite-target relationships was extracted from GutMGene database. Lastly, coronascape module in Metascape database is used for gene annotation and enrichment analysis in various host cells and tissues after SARS-CoV-2 infection. The results indicated that, in comparison to healthy people, *A. muciniphila* was significantly elevated in COVID-19 patients. This bacterium was found to be associated with heightened expression of IL-10, TLR2, TLR4, CLGN, CLDN4, TJP2, and TJP3, while concurrently experiencing a reduction in the expression of IL-12A and IL-12B in humans. The regulatory genes of *A. muciniphila* primarily enhance responses to viruses and cytokines, positively regulate cell migration, and control epithelial cell proliferation. Our study revealed a significant increase in the gut commensal *A. muciniphila* in COVID-19 patients. This bacterium can modulate host immune responses and may also serve as a probiotic with antiviral properties.

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Introduction

Coronavirus disease (COVID-19) is a pandemic disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to the World Health Organization (WHO) as of November 2023, there have been over 772.17 million confirmed cases and 6.98 million deaths worldwide (https://covid19.who.int). Common clinical manifestations of the respiratory tract include dry cough, sore throat, shortness of breath, and systemic fever [1]. Furthermore, extrapulmonary symptoms such as gastrointestinal, neurological, cardiological, and skin manifestations are also increasingly observed [2,3]. Around 5–39.9% COVID-19 individuals had gastrointestinal (GI) manifestations such as diarrhoea, nausea, vomiting, anorexia, and abdominal pain [4–6]. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors to invade human host cells, and ACE2 gene is highly expressed in the alveolar and intestinal epithelium [7,8].

The GI tract is considered to be the largest immune organ in humans and plays an important role in combating infections of pathogens [9]. According to reports, intestinal microorganisms play a crucial role in the pathogenesis of influenza virus infection [10]. Numerous clinical studies have shown that the presence of SARS-CoV-2 load in stool samples is associated with changes in gut microbiota composition in patients with COVID-19 [11,12] suggesting that the components of the bacteriome are affected by SARS-CoV-2 infections and vice versa [13]. It is described that COVID-19 patients faecal had lower levels of IL-10 and higher levels of IL-8 than uninfected controls, while higher levels of faecal virus-specific IgA and IL-23 correlate with more severe COVID-19 [14]. Gut dysbiosis in COVID-19 could contribute to regulating systemic inflammation and reflecting, or even influencing, disease severity, and recovery processes [15,16].

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Akkermansia muciniphila (*A. muciniphila*), a common colonizer in the intestinal mucus layer, is recognized as a mucin-degrading bacterium [17]. Notably, *A. muciniphila* has been found to adhere to the epithelium and to reinforce the intestinal barrier, making it a promising candidate for the next generation of probiotics [18,19]. Numerous studies have found that *A. muciniphila* improved the host metabolic functions and immune responses [20,21]. *A. muciniphila* can generate acetate and propionate that may have anti-inflammatory and antioxidant properties [22,23]. A comprehensive body of research has consistently demonstrated that *A. muciniphila* plays a beneficial role in host defence against various diseases and the ageing process [24,25]. A previous study found that *A. muciniphila* was significantly enriched in mice infected with H7N9, and oral administration of this bacterium notably reduced pulmonary viral titres and levels of pro-inflammatory factor (IL-1β and IL-6) while elevating the levels of anti-inflammatory factor (IFN-β, IFN-γ, and IL-10) in H7N9 infected mice [26]. The study suggested that *A. muciniphila* play an anti-inflammatory and immunomodulatory role in anti-influenza virus [27].

A previous report showed that the abundance of family *Akkermansiaceae* was significantly increased in k18-hACE2 mice, while the decreased abundance of *A. muciniphila* was correlated to disease severity [28]. Furthermore, several clinical studies report that compared with non-COVID-19 individuals, the composition of gut microbiota was significantly altered in patients with COVID-19 [15,16,29–31]. Two studies indicated a significant increase in the abundance of *A. muciniphila* among COVID-19 patients [15,16]. Consequently, we conducted a deeper evaluation of *A. muciniphila's* impact on the pathogenicity of SARS-CoV-2 infection and explored the potential mechanisms behind these effects.

Materials and methods

GMrepo database

GMrepo is a database of curated and consistently annotated human gut metagenomes. The function of the database is to increase the reusability and accessibility of human gut metagenomic data, and enable cross-project and phenotype comparisons. The latest version of the GMrepo v2 contains 353 projects and 71,642 runs/samples, which were obtained by 16S rRNA amplicon and whole-genome metagenomics sequencing, respectively. About 232 COVID-19 patients and 150 healthy people were included. Linear discriminant analysis (LDA) effect size (LEfSe) analysis was conducted on microbial biomarkers from microbiome data, and LEfSe (LDA score > 3.0, $p < 0.05$) was used to identify taxonomic differences.

GutMGene database

GutMGene is a comprehensive database for target genes of gut microbes and microbial metabolites in humans and mouse. The database manually extracted microbe-metabolite, microbe-target, and metabolite-target relationships from almost 400 publications, where they can produce systemic effects on the host by activating or inhibiting gene expression. GutMGene database provides a user-friendly interface to browse, retrieve each entry using intestinal microbiota, metabolite, gene and substrate measures. The microbes and diseases of GutMGene are standardized via disease ontology and the NCBI taxonomy database.

Gene-expression omnibus (GEO) database

The Gene Expression Omnibus is a public repository for next-generation sequence and high-throughput microarray functional genomic data sets submitted by the research community. Public expression datasets with the intestinal transcriptional host response organoids upon exposure to *A. muciniphila* in mice was gathered from GEO. GEO2R, an R-based web application that helped users analyse GEO data, identified the differentially expressed genes (DEGs).

Metascape

Metascape is web-based portal to provide a comprehensive gene list annotation and enrichment analysis. The coronaspace module contains 20 articles and over 360 SARS-CoV-2-related gene or protein datasets, encompassing seven diverse omics technologies such as transcriptome, proteome, phosphorylated proteome, ubiquitinome, and protein-protein interaction. The Coronascape module enables users to submit their own gene data for comparison with publicly available data. Subsequently, metascape is applied to the generated list group for comprehensive data analysis, including signal pathway, gene ontology (GO), and network analysis. In addition, bubble plot of GO and pathway enrichment results are plotted by http://www.bioinformatics.com.cn, a free online platform for data analysis and visualization.

Results

We first analysed the difference of gut microbiota composition between COVID-19 patients and healthy individuals based on GMrepo database. The taxonomic plot results revealed that *Bifidobacterium, Ruminococcus, Faecalibacterium, Eubacterium, Coprococcus,* and *Klebsiella* were depleted in COVID-19 samples, whereas *A. muciniphila's* relative abundance was significantly elevated in COVID-19-positive individuals at the species and genus level (Figure 1(a,b, c)). The comprehensive analysis results also showed that the abundance of *A. muciniphila* was significantly increased in COVID-19 patients than the healthy individuals ($p < 0.01$, Figure 1(d)).

Through GutMGene database, we retrieved previously four previously published literatures on gene expression regulation in humans by *A. muciniphila* [32–35]. The results showed that the bacterium was associated with up-regulated expression of IL-10, TLR2, TLR4, CLGN, CLDN4, TJP2, and TJP3 and down-regulated expression of IL-12A and IL-12B in humans (Figure 2). It was also confirmed that the main metabolites of *A. muciniphila* in humans were propionate and acetate (Figure 3).

Furthermore, coronaspace module of Metascape database was used to conduct pathway process and enrichment analysis of DEGs regulated by *A. muciniphila* in humans. Based on the best matching principle, the data regarding genomic changes in COVID-19 peripheral blood mononuclear cells (PBMCs) from coronaspace is utilized for comparison and functional pathway enrichment analysis with the target gene list. Out of the top 20 enriched pathways obtained through GO pathway analysis, six involve *A. muciniphila* regulatory genes, encompassing response to virus, response to cytokine, positive regulation of cell migration, regulation of epithelial cell proliferation, and leukocyte activation (Figure 3).

Three pooled transcriptomic datasets (GSE18587, GSE126730 and GSE59644, Table S1) of mouse intestinal tissue, fed or cultured with *A. muciniphila* in GEO database, were analysed for differentially expressed genes using GEO2R tool. The GEO2R analysis results showed that these were no DEGs in GSE18587 and GSE126730 datasets based on an adjusted $p < 0.05$ (Figure S1& and; S2). In GSE59644 dataset, we identified 968 DEGs, including 543 up-regulated genes and 425 down-regulated genes (Figure 4(a,b), Table S2). The biological mechanisms and pathways of the DEGs were enriched in response to virus, positive regulation of cell migration, type II interferon signalling, leukocyte differentiation, cell-substrate adhesion, transferrin transport, and regulation of apoptotic signalling pathway (Figure 4(c)).

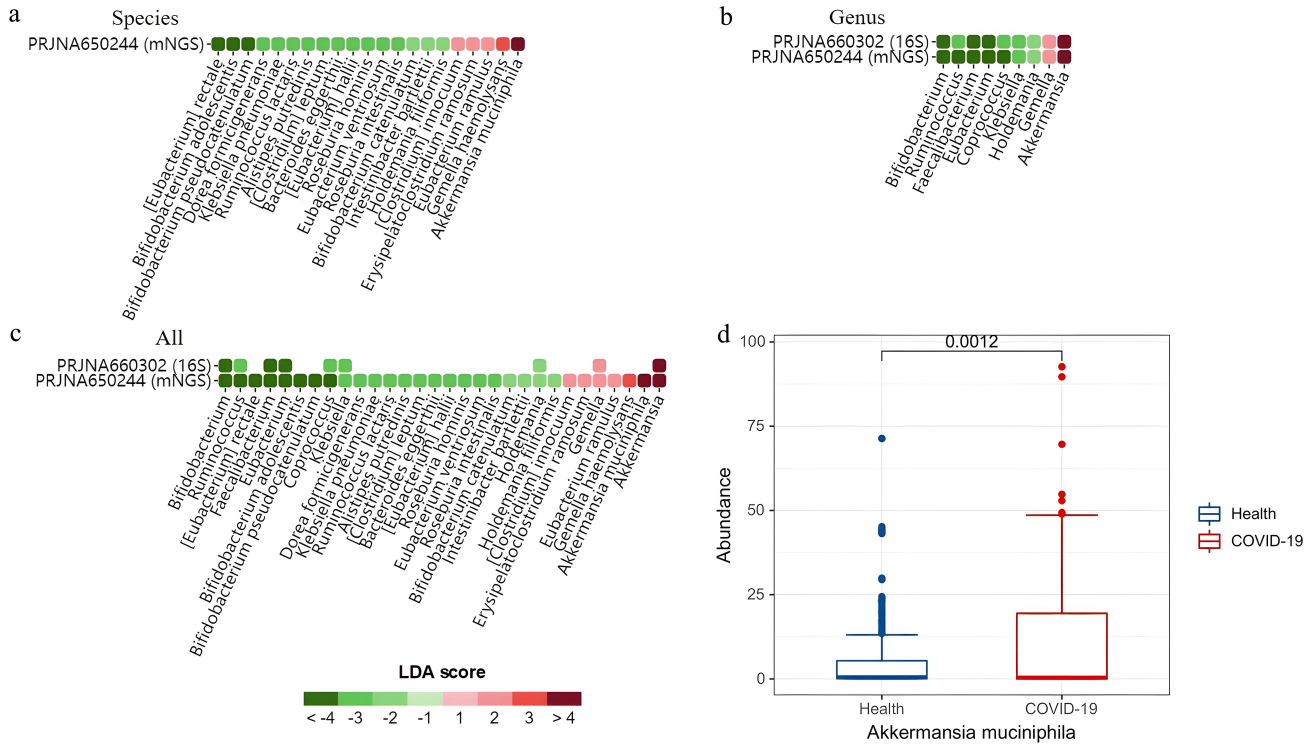

Figure 1. The microbiota relative abundances at the species and genus level of the healthy and COVID-19 patients from the GMrepo database. LDA: linear discriminant analysis, LDA < 0 are health enriched, while those with LDA > 0 are COVID-19 enriched.

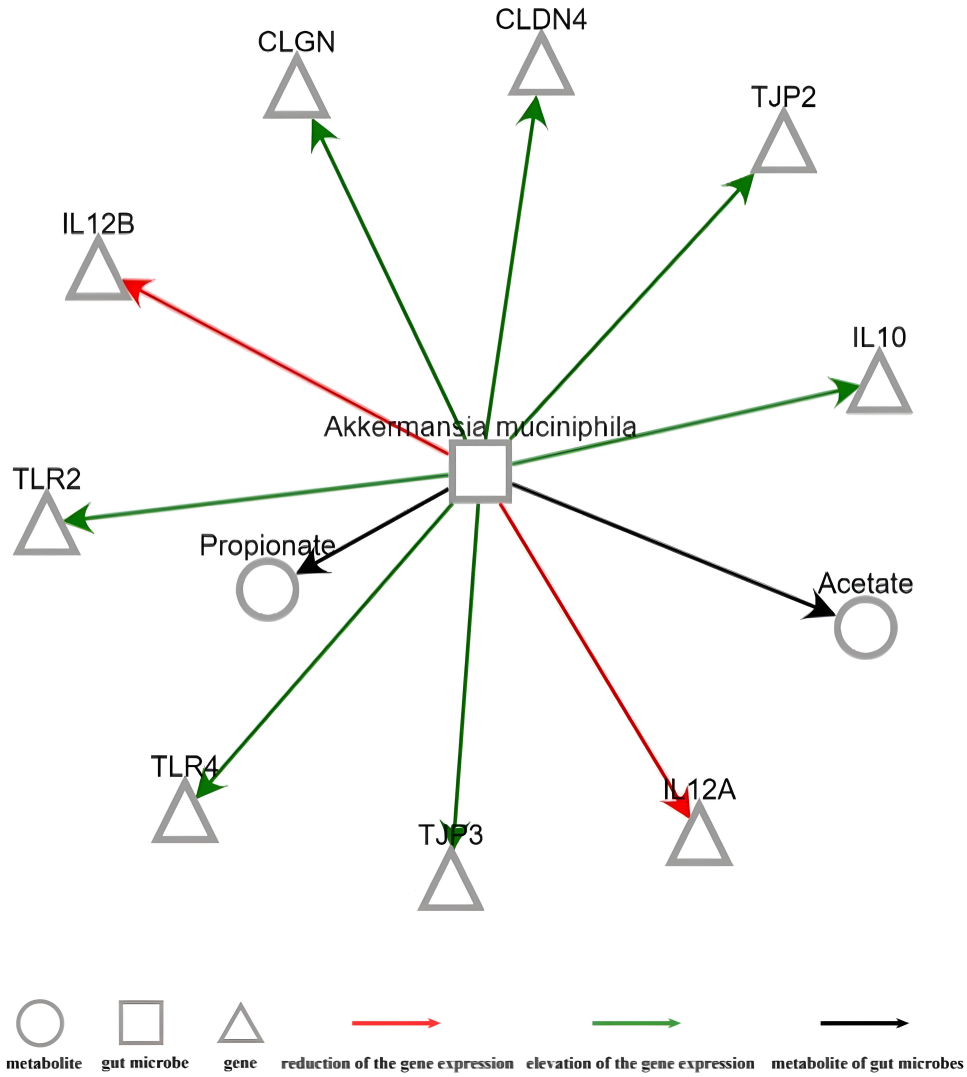

Figure 2. The related regulatory genes and metabolites of *Akkermansia muciniphila* based on GutMGene database.

Discussion

Pathological changes and symptoms caused by COVID-19 extend beyond the respiratory tract, with gastrointestinal manifestations such as abdominal pain and diarrhoea being common sequelae. The gut is one of the most diverse and densely populated organs, with a bacterial to human cell ratio of approximately 1:1 in the adult body [36]. Several studies have reported that gut microbiome of COVID-19 patients is significantly altered compared with to that of healthy individuals [15,16,29–31], suggesting that dysbiosis may have a role in the pathogenesis of COVID-19. Our research has found that *A. muciniphila* was significantly increased in COVID-19 individuals compared with the normal people based on the GMrepo database. This bacterium is known to regulate mucosal microbial networks and improve intestinal barrier function [23,37]. *A. muciniphila* has also been shown to reduce endotoxin levels in mice on high-fat diets and regulate host immune function [20,38]. Therefore, the bacterium is considered a beneficial probiotic [33,37,39].

A. muciniphila has been show to induce the production of IL-10, IL-6, and IL-1β in human-derived PBMCs, demonstrating a wide range of immunomodulatory responses in vitro. This indicated that *A. muciniphila* cannot be strictly defined as pro-inflammatory or anti-inflammatory; instead, it may play a complex role in maintaining the balance of the gut ecosystem [33,40]. Live *A. muciniphila* and pili-like protein *Amuc_1100* induce higher amounts of IL-10 compared to *F. prausnitzii* and *L. plantarum*, suggesting a greater anti-inflammatory capacity for *A. muciniphila* [33,41]. Furthermore, *A. muciniphila* stimulates diverse immune responses and leads to relatively higher upregulation of gene expression in

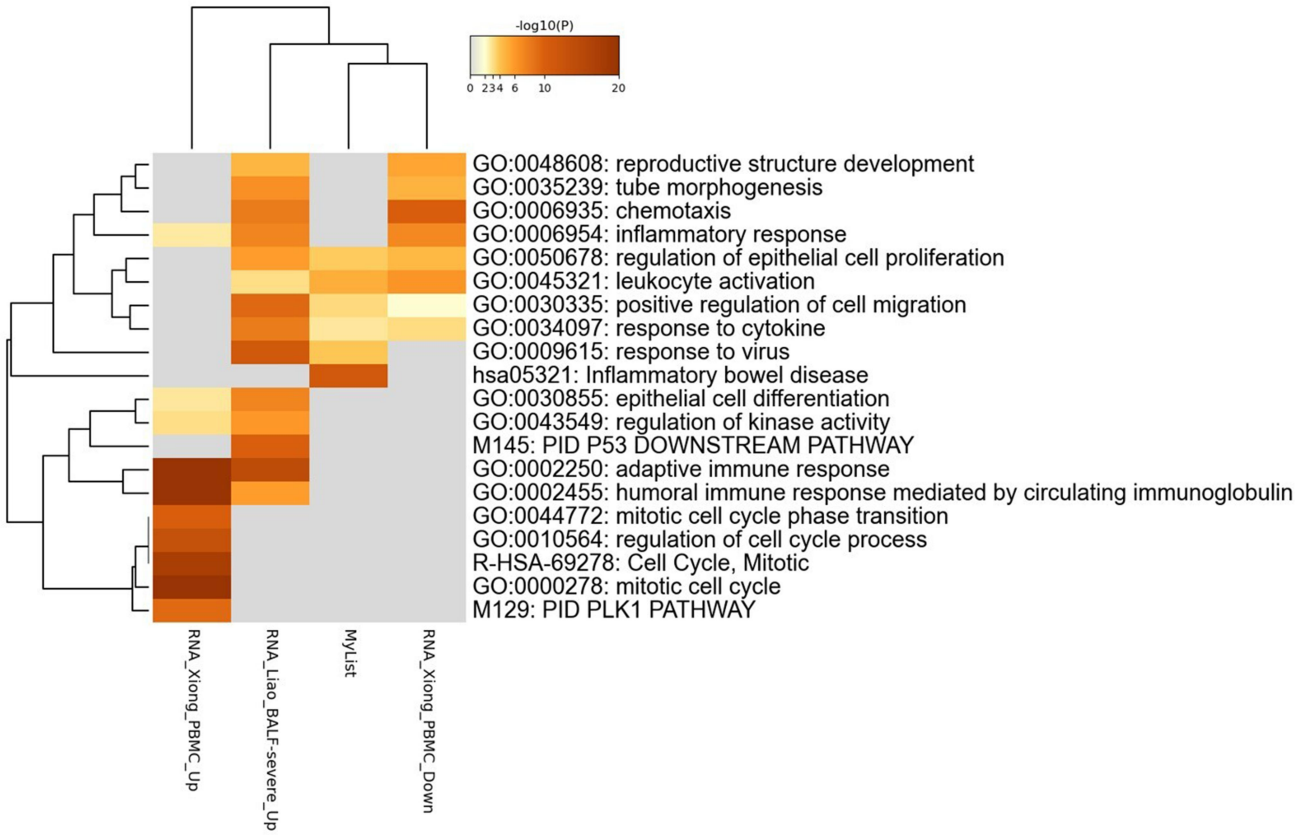

Figure 3. The enrichment analysis of DEGs regulated by *Akkermansia muciniphila* based on coronaspace module of Metascape database. DEGs: differentially expressed genes.

immune response signalling and the ERK/MAPK signalling pathways, indicating a level of gut immune tolerance towards *A. muciniphila* [21]. In addition, *A. muciniphila* and its mucin-derived protein *muc_1100* have been shown to increase trans-epithelial resistance in Caco-2 cells, suggesting an improvement in gut barrier function [33,42]. Research has demonstrated that *A. muciniphila* can exert competitive inhibition against pathogenic microorganisms and may be considered for the treatment of viral infections, indicating its potential as a probiotic [27,43]. The presence of A. muciniphila in the gut can reduce microbial translocation and inflammation in individuals living with HIV, earning it the title of "sentinel of the gut" [44]. Another study identified a lipid from the cell membrane of *A. muciniphila's* (a15:0-i15:0 PE) with immunoregulatory effects, providing a molecular mechanism for its ability to modulate immune responses and its diverse roles in health and disease [45]. In short, *A. muciniphila* is known to regulate immune function, enhance the synthesis of antimicrobial peptides, and promote gut homoeostasis [46].

Studies have increasingly highlighted the mutual regulation between the gut microbiota and viruses, both directly and indirectly. One study reported that the abundance of *Akkermansia* positively correlated with influenza H7N9 infection in vivo; however, oral administration of *A. muciniphila* significantly reduced weight loss, mortality, and viral titres in mice [26]. This suggests that *A. muciniphila* may be a potential anti-influenza probiotic. A recent report showed that *A. muciniphila* became more prevalent during the peak of SARS-CoV-2 infection in hACE2 mice challenged with a high virus dose. Despite being challenged with the same virus dose, these mice exhibited reduced clinical signs throughout the infection, suggesting that the decreased abundance of this bacterium may be correlated with disease severity [28]. Meanwhile, *A. muciniphila* aids in restoring a healthy microbiota and plays a role in protecting epithelial cells in the gut. Administration of the bacterium may enhance the intestinal barrier by increasing the expression of *zonula occludens-1* and *occludin* [24,47]. Additionally, *A. muciniphila* repairs intestinal mucosal damage by restoring the number of goblet cells and increasing the expression of *mucin-2* [48–50]. Our research indicates that *A. muciniphila* can upregulate the expression of genes related to antiviral pathways, suggesting that

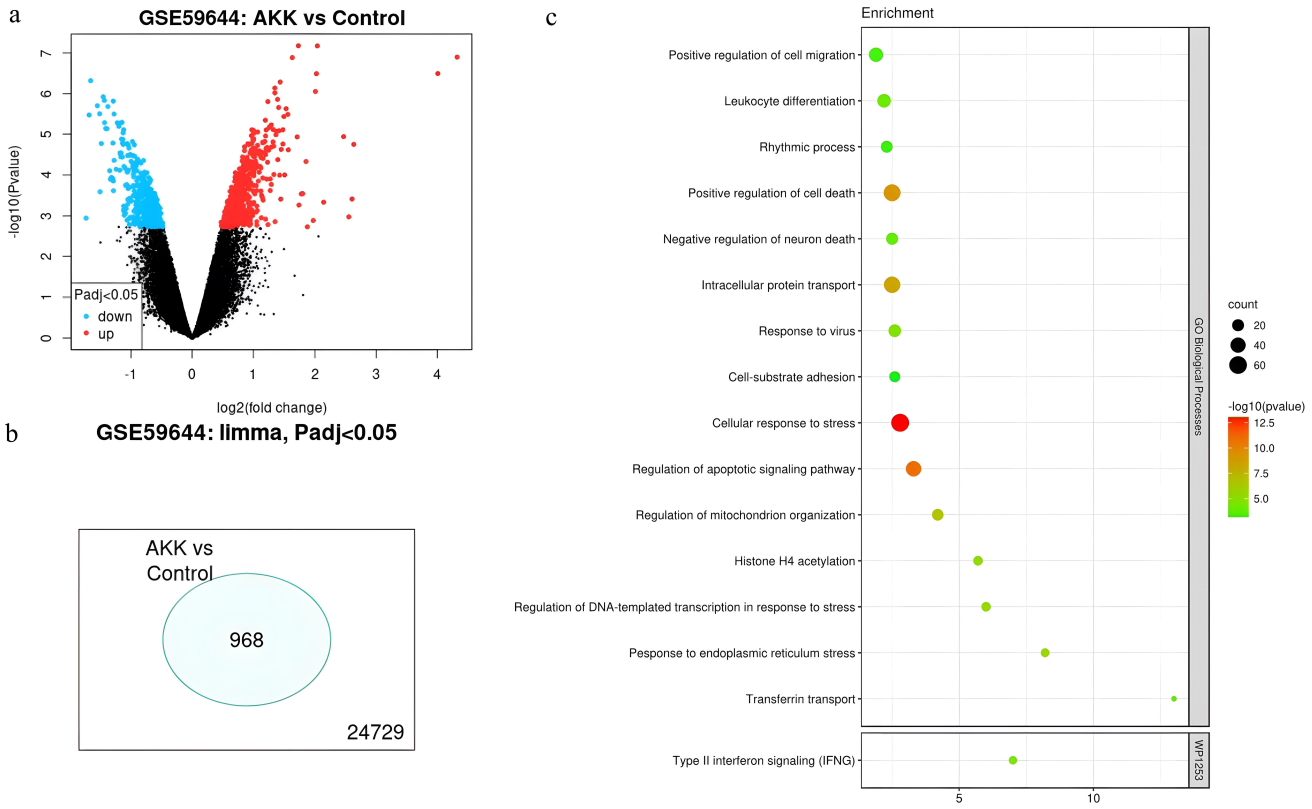

Figure 4. The intestinal tissue DEGs and pathway analysis between *Akkermansia muciniphila* pretreated-mice and controls. DEGs: differentially expressed genes, AKK: *Akkermansia muciniphila*.

the bacterium administration may play a role in resisting viral infections.

On the other hand, metabolites derived from gut microbiota can regulate immune responses and mitigate enteric viral infections [51]. The primary bacterial metabolites involved in regulating viral infections are short-chain fatty acids (SCFAs), flavonoids, and bile acids. SCFAs play a role in immune regulation by inducing the production of immunoglobulins, which have anti-inflammatory effects [52]. A reduction of SCFAs may be associated with a pro-inflammatory state and also down-regulation of intestinal ACE2, thus potentially increasing susceptibility to COVID-19 [53–55]. *A. muciniphila* is capable of producing acetate and propionate, which are the main components of SCFAs. Acetate, in particular, may reduce the production of pro-inflammatory cytokines while increasing cytokine production in T cells, thereby potentially enhancing the immune response during infections or other stressful conditions [56,57]. Evidence also suggests that acetate can improve pathological outcomes during respiratory syncytial virus infections by enhancing antiviral response [58]. However, a recent study found that while the reduction of SCFAs is relevant to SARS-CoV-2 infection, SCFA supplementation did not reduce SARS-CoV-2 replication in the lungs or ameliorate gut inflammation in a COVID-19 hamster model [55]. Therefore, the potential effect of SCFAs on COVID-19 requires further investigation.

A study demonstrated that abundance of *A. muciniphila* increased during the course of thrombocytopenia syndrome caused by phlebovirus infection and was significantly reduced in deceased patients compared to survivors. This finding suggests that the bacterium may play a protective role against phlebovirus infection [59]. Moreover, surviving patients exhibited significantly reduced expression of IL-1β, IL-6, and TNF-α in serum, which were negatively correlated with the abundance of *A. muciniphila*. Another study reported that supplementation with live *A. muciniphila* produced a novel tripeptide, Arg-Lys-His (RKH), and significantly reduced sepsis-induced mortality in piglet models, highlighting the preventive effects of *A. muciniphila* and its metabolite RKH against sepsis-induced systemic inflammation and organ damage [60]. Additionally, previous study suggested that severe COVID-19 patients with higher abundance of intestinal *A. muciniphila* had a better prognosis compared to those with lower levels [11]. These studies indicate a potential cross-talk between gut microbiota and the

host's immune response to enteric viruses. Therefore, future investigations are needed to elucidate the molecular links between host anti-inflammatory responses and gut microbiota, along with its metabolites, in the context of systemic viral infections.

Some observational studies have found that the abundance of intestinal *A. muciniphila* abundance in COVID-19 patients does not significantly differ from that in healthy individuals [10,11,31]. Furthermore, *A. muciniphila* administration slightly increased creatine kinase levels in healthy volunteers, suggesting a potential regulatory role of the bacterium in cardiovascular disease [61]. Additionally, previous reports indicated that the abundance of *A. muciniphila* was increased in severe COVID-19 cases and was positively correlated with elevated levels of creatine kinase isoenzyme and aspartate transaminase [62]. Two studies also showed that *A. muciniphila* was positively correlated with plasma concentrations of IL-1β, IL-6, and IL-8 in a COVID-19 cohort, suggesting that the bacterium could potentially influence disease severity and outcomes [16,63]. Due to varying sample sizes and different detection methods for gut microbiota in published studies, inconsistent research results have been reported. Therefore, the actual effect of *A. muciniphila* in COVID-19 patient needs to be validated in larger cohorts and appropriate animal models at different stages of the disease.

A recent study used proteomic biomarker data to construct blood proteomic risk score (PRS), and found that it was positively related to the poor prognosis of COVID-19, suggesting that PRS can be used as a biomarker for the prognosis of severe COVID-19. This study further discussed the relationship between gut microbiota and the COVID-19 related PRS mentioned above, and the results showed that the loss of gut microbiota was closely related to proteomic biomarkers, and changes in gut microbiota indicators preceded changes in blood proteomic biomarkers [64]. Other studies have highlighted that the systemic effects of COVID-19 are not only determined by the direct action of the virus but also significantly modulated by host metabolic and microbiome profiles [65,66]. These studies indicate that the critical role of systemic biological networks in understanding and treating COVID-19, showcasing the power of omics technologies in unravelling complex disease mechanisms.

In conclusion, our study revealed that the abundance of the gut commensal *Akkermansia muciniphila* was significantly increased in COVID-19 patients. *A. muciniphila* may modulate host immune function and potentially exert antiviral effects as a probiotic.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Author contributions

ZMD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Writing – original draft. MLX: Data curation, Formal analysis, Funding acquisition, Investigation, Software, Visualization, Writing – original draft. QQZ: Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft. BZ: Formal analysis, Methodology, Resources. JZW: Investigation, Validation. QL: Investigation, Validation. YL: Investigation, Validation. HBL: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. All authors have read and approved the final version of the manuscript.

Consent for publication

All authors have reviewed the final version of the manuscript and approved it for publication.

Data availability statement

The dataset supporting this study is openly available in FigShare at https://doi.org/10.6084/m9.figshare.26536585.

Ethical approval

This study analysed de-identified, publicly available data from publicly available databases (GMrepo, GutMGene, and GEO). The Medical Ethics Committee of the First People's Hospital of Xianyang reviewed this project and determined it exempt from ethics approval (Exemption Reference No.: LC-HM-2025001) in accordance with 45 CFR 46.104(d)(4) & Article 24 of China's Ethical Review Measures. All data usage complies with public databases' terms of access and the ethical standards of the original data-generating studies.

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