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Propionate alleviates ulcerative colitis by modulating the PI3K/AKT signaling pathway and suppressing NLRP3 inflammasome activation†

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Background: Ulcerative colitis (UC) poses a significant health challenge characterized by recurrent inflammation of the intestinal tract, yet effective treatment options remain elusive. While previous studies have hinted at the potential of propionate, a short-chain fatty acid (SCFA), in mitigating colitis, the underlying mechanism remains unclear. *Purpose*: This study aims to elucidate the therapeutic effects of propionate in dextran sulfate sodium (DSS)-induced colitis and explore its regulatory influence on the NLRP3 inflammasome and associated signaling pathways. *Methods: In vivo*, we employe two kinds of DSS-induced colitis model to examine propionate's impact on the NLRP3 inflammasome. Additionally, *in vitro* investigations were conducted using the RAW264.7 cell line. *Results*: Our findings present compelling evidence that propionate effectively ameliorates DSS-induced colitis by impeding NLRP3 inflammasome activation. This intervention leds to a reduction in pro-inflammatory factors, restoration of the epithelial barrier, and downregulation of the PI3K/AKT signaling pathway. Notably, these effects are mediated through the activation of its receptor GPR43. *Conclusions*: This pioneering study establishes propionate as a potent agent in alleviating UC by suppressing NLRP3 inflammasome activation. The propionate-NLRP3 axis emerges as a promising therapeutic target for inflammatory diseases, opening new avenues for treatment strategies in UC.

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1. Introduction

Ulcerative colitis (UC) is a pervasive and persistent inflammatory condition affecting the intestinal tract.[1] The global prevalence of UC has exhibited a consistent rise in numerous countries, underscoring the urgency of understanding its underlying mechanisms.[1–4] Among the pivotal pathogenic factors contributing to UC, the hyperactivation of the innate immune response, particularly inflammatory bursts, appears to play crucial role in disease progression.[5] Within this context, the inflammasome – an innate immune receptor – holds significance as a regulator of intestinal homeostasis.[6–8] Importantly, aberrant inflammasome hyperactivation has been closely associated with various diseases, including Alzheimer's disease, UC, diabetes mellitus, and atherosclerosis.[9–12] The nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) inflammasome has been extensively studied.[13] Activation of the NLRP3 inflammasome has been linked to the production of reactive oxygen species (ROS), lysosomal damage, and mitochondrial dysfunction.[14] Notably, studies have implicated NLRP3 in UC susceptibility, revealing elevated levels of NLRP3 and interleukin-1β (IL-1β) in UC patients and mice, while symptoms were amelio-

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rated in NLRP3$^{-/-}$mice.[15,16] Consequently, targeting the hyperactivation of the NLRP3 inflammasome emerges as a potential therapeutic strategy for UC.[17]

In addition to immune dysregulation, the microbiota and its metabolites have been recognized as pivotal modulators of UC pathogenesis, impacting fundamental physiological processes such as immune regulation and gut barrier function.[18–21] Notably, increased intake of dietary fibers and short-chain fatty acids (SCFAs), among the myriad bacterial metabolites in the gut, have demonstrated clinical benefits of for UC patients.[22,23] Of particular interest, propionate, an abundant SCFA closely associated with the mucus layer of intestinal epithelial cells, has shown promise in improving gut barrier function and suppressing inflammation.[24] Propionate had a role in intestinal mainly through SCFAs receptor 43 (G protein-coupled receptor 43, GPR43). GPR43 deficiency caused impaired gut epithelial barrier function, reduced the expression of mucins and antimicrobial peptides and increased the susceptibility of mice to bacterial infection.[25,26] Moreover, SCFAs restored gut barrier function by inhibiting NLRP3 inflammasome and autophagy.[27,28] Propionate plays a crucial role in regulating the SCFAs/GPR43/NLRP3 pathway.[29] Notably, propionate alleviates LPS-induced acute respiratory distress syndrome in rats by inhibiting the activation of the PI3K/AKT/mTOR signaling pathway, promoting autophagy, and reducing the production and release of inflammatory markers.[30] Furthermore, activation of the PI3K/AKT pathway increases the expression of NLRP3, thereby enhancing the expression of inflammatory cytokines.[31] However, it remains unexplored whether the intervention of propionate can influence the PI3K/AKT signaling pathway through its receptor GPR43 to inhibit the activation of the NLRP3 inflammasome, thereby alleviating the progression of UC.

Here, we aim to elucidate the protective effects and underlying mechanisms of propionate in DSS-induced colitis, focusing on its ability to inhibit NLRP3 inflammasome activation and the subsequent release of proinflammatory factors, such as IL-1β and IL-18. Critically, we also found that propionate downregulates the PI3K/AKT signaling pathway through its receptor GPR43 to inhibit NLRP3 inflammasome activation, thereby improving DSS-induced colitis. These results provide valuable insights into restoring epithelial barrier integrity and suppressing the development of UC.

2. Materials and methods

2.1. Reagents

Lipopolysaccharide and propionate (≥99%) are provided from Sigma-Aldrich (St Louis, CA). Dextran sulfate sodium (DSS, MW 40 000) is obtained from MP Biomedicals (Irvine, CA, USA). Antibodies are sourced from Abcam (Cambridge, UK), Cell Signaling Technology, Inc. (Beverly, MA, USA), and Proteintech (Wuhan, China). Mouse enzyme-linked immunosorbent assay (ELISA) kits are acquired from Mlbio (Shanghai, China).

2.2. Cell culture

The role of propionate on macrophages is validated *in vitro* using the RAW264.7 cell line. RAW264.7 cells are obtained from Cell Life Science & Technology (Wuhan, China) and cultured in DMEM supplemented with 10% heat-inactivated FBS and 1% penicillin–streptomycin solutions (Gibco, Foster City, CA) in a humidified incubator with 5% CO_2 at 37 °C. The RAW264.7 cells are activated with LPS (100 ng ml^{-1}) for 6–8 h, with or without propionate (0.3, 0.6, 1 mM) for 2 h.

2.3. Experimental animals

Wild-type C57BL/6J mice are purchased from Beijing Vital River Laboratory Animal Technology and housed in the Animal Center of Tsinghua University. All animals are housed underd in standard laboratory conditions with a 12 h light/dark cycle specific pathogen-free facility with an average ambient temperature of 22–24 °C and an average humidity of 48% at the Animal Center of Tsinghua University. All mice (7-week-old males) are randomly grouped and all experimental procedures were conducted at the Animal Center of Beijing, approved by the Medical Ethics Committee for Experimental Animals, Tsinghua University School of Life Science (THU-02-2023-079A).

An acute colitis model was employed using classical methods. Mice were given 3% DSS (36–50 kDa, colitis grade MP Biomedicals) in filter-purified drinking water *ad libitum* for 6 days, followed by a resumption of normal water intake. To evaluate the protective efficacy of propionate against colitis in mice, 7-week-old C57BL/6J mice were treated with or without 50 or 100 mM propionate administered in drinking water *ad libitum* for 10 days. The specific experimental groups were as follows: (1) control, (2) DSS, (3) 50 mM propionate + DSS, (4) 100 mM propionate + DSS. The incidence of symptoms such as hair erection and fatigue, weight loss, and rectal bleeding in the mice were monitored daily. Fecal changes and rectal bleeding were recorded for each mouse to assess the disease activity index (DAI) score, as previously described.[32]

2.4. Histopathology and Alcian blue/periodic acid-Schiff staining

Colon tissues are harvested post-sacrifice, fixed in 4% paraformaldehyde, and processed for hematoxylin & eosin (H&E) and Alcian blue-periodic acid-Schiff (AB-PAS) staining. Digital images are acquired using a Zeiss fully automated digital slide scanner (Axio Scan. Z1 Zeiss).

2.5. TUNEL staining

Intestinal segments are processed at terminal endpoint for apoptosis detection using the TUNEL apoptosis kit. The procedure included dewaxing, protease K repair, membrane breaking, TUNEL reaction solution incubation, DAPI staining, film sealing, and imaging (Axio Scan. Z1 Zeiss). Data analysis is performed using ImageJ software.

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2.6. Transmission electron microscopy (TEM)

Colon tissues (1–3 mm) are quickly excised, fixed in 2.5% glutaraldehyde, osmium tetroxide-stained, dehydrated in ethanol and embedded overnight in epoxy propane wax. After Ultra ultrathin slicing, samples are observed using a Hitachi H-7650B TEM.

2.7. RNA extraction and quantitative real-time PCR

RNA is extracted from colon tissues and cells using the steadypure universal RNA extraction kit (Accurate biotechnology, Co., Ltd, Changsha, China) according to manufacturer recommendations. cDNA is obtained using the Evo M-MLV RT mix kit. SYBR Green premix pro Taq HS qPCR kit is used for amplification. Primers sequences provided in Table 1 are synthesized by Accurate Biotechnology (Changsha, China).

2.8. Enzyme-linked immunosorbent assay (ELISA)

Inflammatory cytokine concentrations in colon tissues are determined using a mouse ELISA kit (Mlbio, China). Standard procedures are followed, and values are measured at 450 nm using EnVision (Perkin).

2.9. Western blotting analysis

Cells and colonic tissues are lysed in cold RIPA buffer (Beyotime Biotechnology) with PMSF and phosphatase inhibitor. Protein samples are separated by electrophoresis, transferred to PVDF membranes, and probed with primary and secondary antibodies. Chemiluminescence signals are obtained using the ECL kit, and gray values are calculated with Image J.

2.10. Transcriptome RNA-seq analysis

Transcriptome sequencing is performed by Novogene (Beijing, China). Differential gene expression is analyzed for Hierarchical clustering and KEGG pathway analysis using R software, with a corrected p-value of 0.05 as the threshold.

2.11. Small interfering RNA (siRNA)

The RAW264.7 cells are seeded at 40% confluence in 12-well plates, and transfected with Scrambled (Scr) siRNA or GPR43 siRNA (GenePharma, Shanghai, China) using Lipofectamine™ 2000 (Thermo Fisher Scientific, USA). Transfection efficiency is confirmed by western blot. The sequence of the siRNA targeting GPR43 is 5′-GGCACUGAGAACCAAAUAATT-3′, and the sequence of the negative control siRNA is 5′-UUAUUUGGUUCUCAGUGCCTT-3′.

Table 1 The primer sequences used in the study as follows

Name	Primer sequence (5′ → 3′)
β-Actin	F primer: TACCACCATGTACCCAGGCA R primer: CTCAGGAGGAGCAATGATCTTGA
NLRP3	F primer: GCTCCAACCATTCTCTGACCAT R primer: GGTTGGTTTTGAGCACAGAGG
IL-1β	F primer: GGCAACCGTACCTGAACCCA R primer: CCACGATGACCGACACCACC

2.12. Statistical analysis

Data are presented as mean ± SD. Unpaired t-tests are employed to compare differences between two groups. One-way ANOVA followed by Newman–Keuls or Dunnett multiple comparisons test are employed to determine significant differences among multiple groups, Pairwise correlation analysis was conducted using Pearson methods, with $p < 0.05$ consideres statistically significant.

3. Results

3.1. Propionate attenuates the symptoms of DSS-induced colitis

Clinical observations have consistently highlighted the recurrent nature of UC, with SCFAs emerging as potential mitigators of UC severity.[23,33,34] The specific impact of propionate, a type of SCFA, has remained relatively unexplored; therefore we explore the protective effects of propionate against UC in mice (Fig. 1A).

Mice subjected to 3% DSS exhibites distinctive features characteristic of acute colitis, as evidenced by substantial weight loss, reduced colon length, severe tissue damage, elevated DAI scores, and an increased spleen-to-weight ratio compared to the control group (Fig. 1 and 2). Furthermore, treatment with varying concentrations of propionate (50 mM, 100 mM) demonstrate a notable improvement in UC development. Strikingly, 100 mM propionate emerges as the most effective concentration, significantly attenuating weight loss, colon shortening and DAI scores (Fig. 1B–E). We also obtain certain results in the long-term 14-day model (Fig. S2A–E†). Administration of 100 mM propionate for a period of 10 days was well tolerated, with mice displayed no significant alterations in colon length and tissue structure compared to untreated controls (Fig. S1†). These results underscore the potential therapeutic efficacy of propionate in treating UC.

3.2. Propionate restores tissue damage and mucosal barrier in DSS-induced colitis

The intricate interplay between intestinal barrier dysfunction and UC has been extensively documented.[35] Disruption of the intestinal epithelial barrier stands out as a hallmark of UC pathology. We next investigate the regulatory effects of propionate on the gut epithelial barrier in DSS-induced colitis.

In comparison to the control group, evident tissue damage is observed in DSS-induced colitis. Strikingly, treatment with 100 mM propionate robustly attenuates ulceration and mucin loss, as vividly demonstrated by H&E and AB-PAS staining (Fig. 2A–C). Building on the potential of propionate to restore mucin loss, western blot analysis provides further evidence of its beneficial impact on the intestinal barrier. Specifically, protein expression levels of MUC2 ($p = 0.0749$) and occludin are elevated in mice treated with 100 mM propionate, reinforcing the notion that propionate plays a pivotal role in preserving gut barrier integrity (Fig. 2D and E). Collectively, our results strongly suggest that propionate contributes to the maintenance of gut barrier integrity in DSS-induced colitis.

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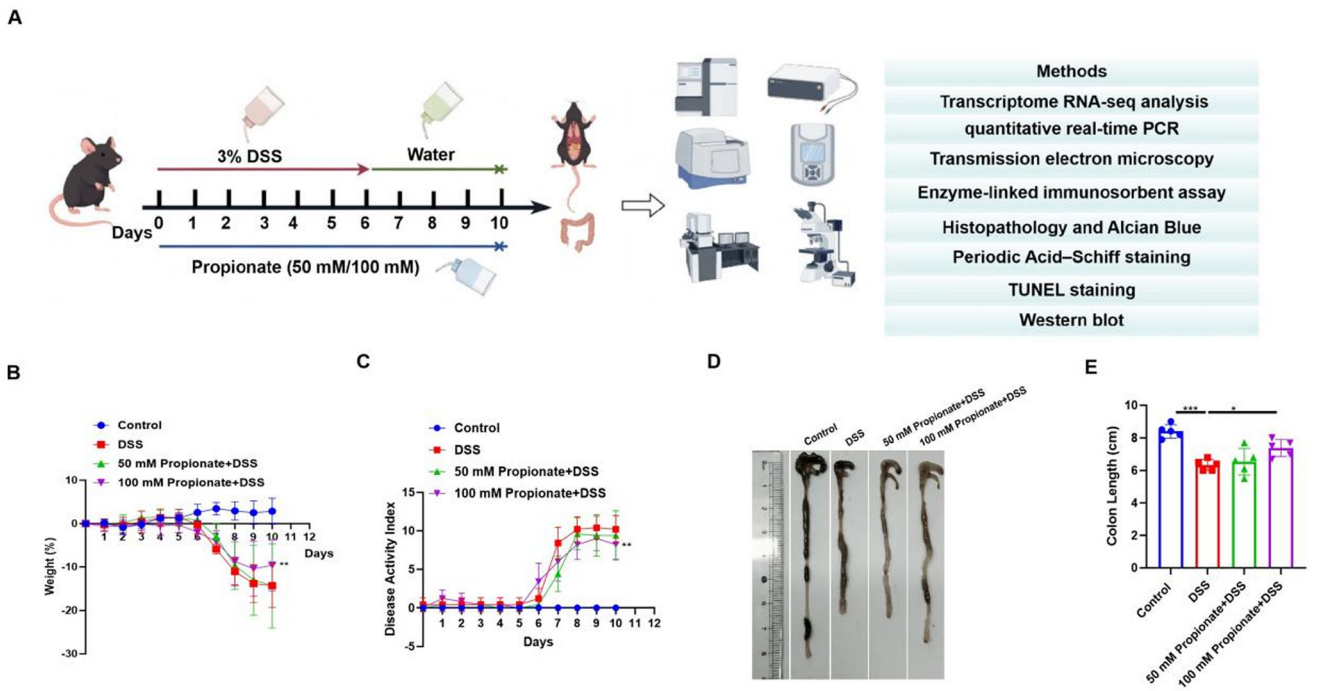

Fig. 1 Propionate ameliorates the symptoms of DSS-induced colitis in mice. (A) Experimental design. Mice are randomly assigned to five groups: DSS, propionate (50, 100 mM) + DSS, and a control group receiving water. (B) Percentage of weight change in each group, demonstrating the impact of DSS and propionate treatment. (C) Assessment of DAI scores to evaluate the clinical severity of colitis in different treatment groups (D and E) colon length in mice from each experimental group, indicative of colitis-induced changes (Newman–Keuls,*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; the data are the mean ± SD, $n = 5$).

3.3. Propionate decreases inflammatory responses in DSS-induced colitis

A local inflammatory burst is a distinctive feature of UC, often accompanied by an elevation of pro-inflammatory factors.[36] Therefore, we then assess the impact of propionate on this inflammatory milieu, and its ability to modulate the expression of pro- and anti-inflammatory factors. ELISA results unveile a substantial increase in the levels of pro-inflammatory cytokines, including TNF-α and IL-1β in the UC condition (Fig. 3A and B). Remarkably, treatment with 100 mM propionate exhibites a clear inhibitory effect on these pro-inflammatory factors while concurrently promoting the expression of the anti-inflammatory factor TGF-β (Fig. 3C), Similarly, western blot analysis confirmes a significant reduction in the protein levels of IL-6 and iNOS in UC mice treated with propionate (Fig. 3D).

3.4. Propionate improves the mitochondrial dysfunction in DSS-induced colitis

Consistent with our observations in Fig. 2, TEM results demonstrate the impact of propionate on the ultrastructural integrity of colonic tissues in DSS-induced colitis. In DSS-induced mice, tight junctions appears loose, broken, with unclear borders and increased intercellular spaces. Strikingly, the 100 mM propionate-treated group exhibites complete tight junctions with clear borders. Additionally, the colon microvilli of DSS-induced mice display shortened length, disorganize arrangement, and sparse distribution, while the 100 mM propionate group exhibites slender, neatly arranged microvilli with a higher density (Fig. 4A).

Mitochondrial dysfunction is recognized as a pivotal factor in the onset and recurrence of UC.[37] Our TEM results further indicate that mitochondria in DSS-induced colitis were characterized by swelling, vacuolization, disrupted bilayer membrane structure, and a reduced number of mitochondrial ridges. Notably, propionate treatment visibly restores these mitochondrial structural abnormalities (Fig. 4B). Mitochondrial oxidative phosphorylation (OXPHOS) can actively protect mice from DSS.[38] Delving into the functional mechanism, our results demonstrate that propionate treatment substantially restores the protein expression of respiratory complexes I, II and V(NADH dehydrogenase, succinate dehydrogenase, FoF1-ATPase), however, it has little effect on the protein expression of complex III, IV (ubiquinol dehydrogenase, cytochrome c oxidase) in UC mice (Fig. 4C). Collectively, these findings indicate that propionate treatment holds the potential to enhance mitochondrial function in the damaged colon, thus contributing to overall tissue recovery.

3.5. Propionate improves the symptoms of colitis by inhibiting PI3K/AKT signaling pathway and reducing NLRP3 inflammasome activation in DSS-induced colitis

To elucidate the role of propionate in the context of UC, we conducted transcriptome sequencing on colon tissues from mice treated with propionate + DSS and DSS alone. We identify

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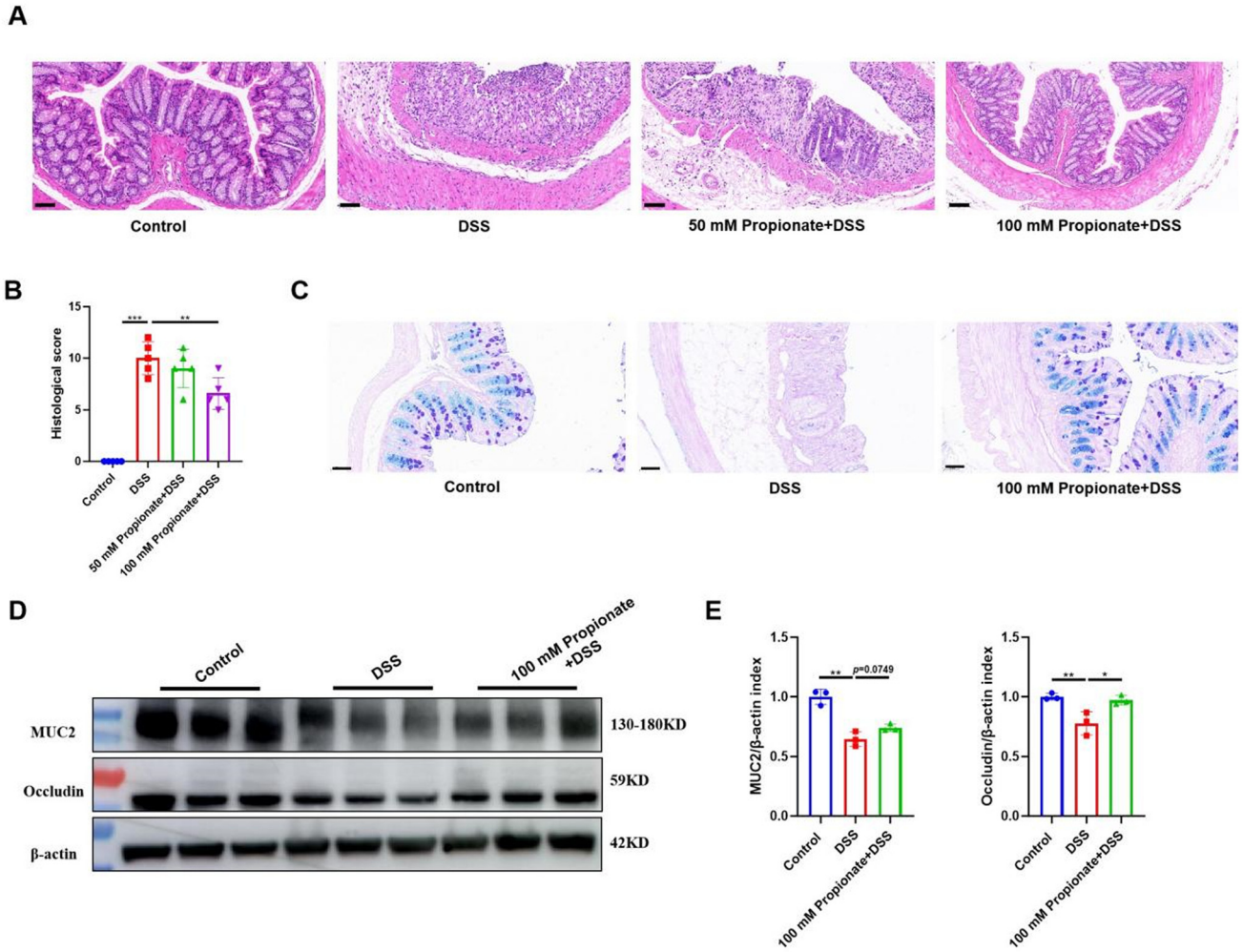

Fig. 2 Propionate mitigates DSS-induced intestinal barrier impairment. Mice are randomly assigned to different treatment groups, and after propionate intervention, colons are excised, sectioned, and subjected to H&E staining (A and B) or AB-PAS staining (C). Scale bar = 50 μm (n = 5). (D and E) Western blots for occludin and MUC2 proteins, with corresponding quantification results (n = 3) (*p < 0.05, **p < 0.01, ***p < 0.001; the data are the mean ± SD).

229 upregulated genes and 697 downregulated genes (Fig. 5A). Hierarchical clustering analysis reveales a distinct difference in gene expression profiles induced by propionate treatment. Notably, NLRP3 inflammasome-related genes are significantly downregulated in the propionate-treated group compared with the DSS group, as indicated by the transcriptome sequencing data (Fig. 5B). These results were experimentally validated by qPCR and western blot analysis (Fig. 6A and B). Additionally, TUNEL staining demonstrates an increase in dead cells in UC mice, while propionate treatment significantly reduces TUNEL-positive cells (Fig. 6D). Collectively, these findings provide compelling evidence that propionate prevents the progression of UC by effectively inhibiting NLRP3/Caspase 1/IL-18/IL-1β signaling.

The KEGG pathway analysis unveiles that propionate treatment induce the enrichment of the PI3K-AKT signaling pathway (Fig. 5C). Building upon this observation and the results from transcriptome sequencing, we formulate the hypothesis that propionate might inhibit inflammasome activation by regulating the PI3K/AKT signaling pathway. We assesse the protein expression of key components in the PI3K/AKT pathway using western blot. The results demonstrate a significant upregulation of the PI3K/AKT signaling pathway in UC mice, while treatment with propionate leds to a notable reduction in the protein expression of PI3K and AKT (Fig. 6C). We find that the inhibitor of PI3K/AKT signaling pathway (LY294002, 10 mg kg^{-1}) reverses the effects of DSS on intestinal symptoms; we also find that LY294002 in combination with propionate are more effective in improving the intestinal symptoms of DSS-induced colitis (Fig. S3A–E†), which may be due to the dual effect of propionate and LY294002 on the PI3K/AKT signaling pathway. This finding provides compelling evidence that propionate ameliorates UC by inhibiting the PI3K/AKT signaling pathway.

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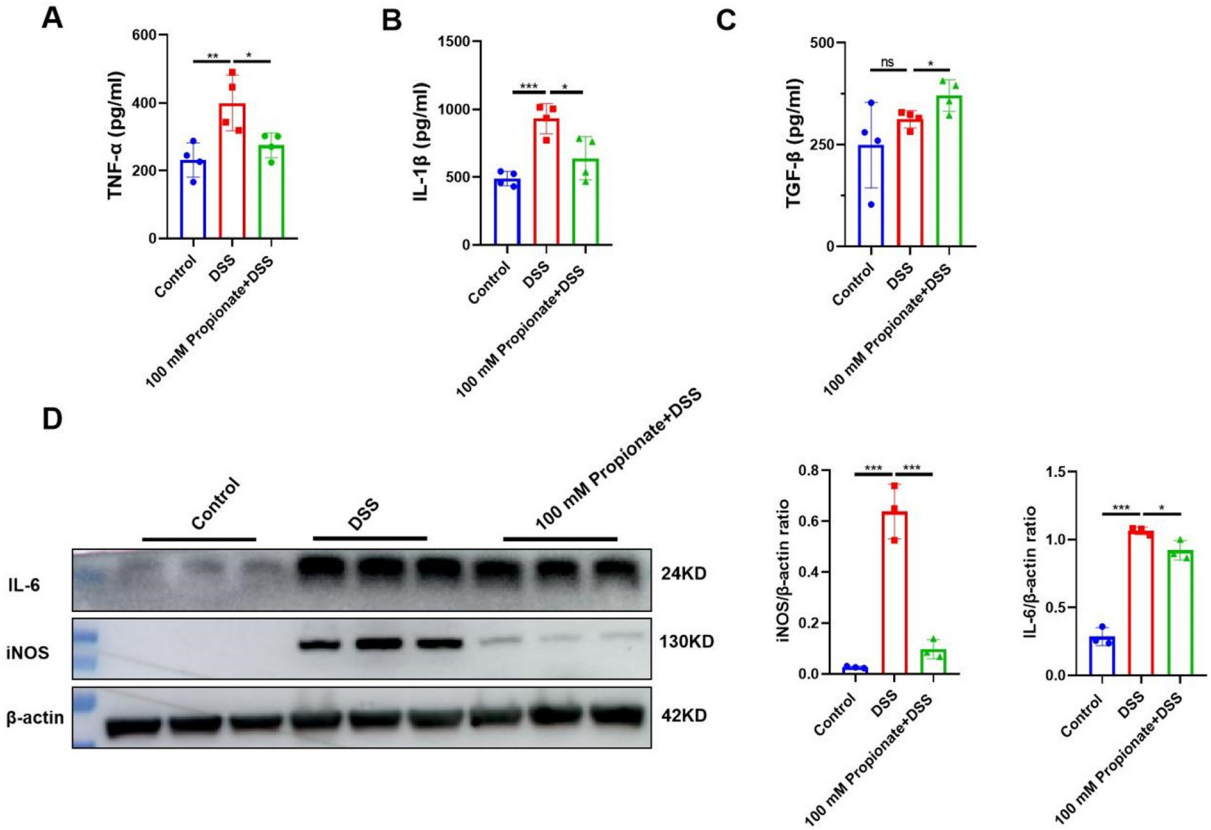

Fig. 3 Effects of propionate on the inflammatory responses in DSS-colitis mice. (A–C) Quantification of the protein expression levels of pro-inflammatory cytokines IL-1β and TNF-α, as well as anti-inflammatory cytokine TGF-β in the colon tissue supernatant following propionate treatment. Data are represented as mean values (n = 4). (D) Protein expression levels of IL-6 and iNOS in colon tissue are assessed by western blot analysis. Data are presented as mean values (n = 3) (*p < 0.05, **p < 0.01, ***p < 0.001; the data are the mean ± SD).

3.6. Propionate prevents NLRP3 inflammasome activation through inhibiting PI3K/AKT signaling pathway in RAW264.7 cells

To further validate the impact of propionate, we next test it *in vitro* in LPS-stimulated RAW264.7 cells. Western blot analysis reveales that 0.3 mM propionate effectively inhibits the upregulation of p-AKT and NLRP3 protein expression induced by LPS (Fig. S4†). Consistently, compared to LPS group, the protein levels of p-AKT, AKT, NLRP3, IL-18, Pro-caspase 1, and Caspase 1 are significantly reduced (Fig. 7A–F), and the mRNA levels of NLRP3 and IL-1β are also significantly reduced with propionate treatment (Fig. 7G and H).

Given the reported involvement of the PI3K/AKT signaling pathway in the regulation of the NLRP3 inflammasome,[39] we use SC79, an AKT agonist, to further elucidate the mechanism underlying propionate's impact on PI3K/AKT signaling pathway and NLRP3 inflammasome. Activating AKT with SC79 increases the protein levels of p-AKT, NLRP3 and IL-18, confirming that propionate reduces NLRP3 inflammasome activation by inhibiting the PI3K/AKT signaling pathway (Fig. S5†). These *in vitro* findings align with our *in vivo* observations, collectively emphasizing the potential of propionate in modulating the PI3K/AKT signaling pathway and subsequently influencing NLRP3 inflammasome activation.

3.7. Propionate exerts the anti-inflammatory effects through GPR43

It was reported that propionate exerted its anti-inflammatory effects through GPR43.[26] We employ siRNA-GPR43 to further elucidate the post-receptor pathway of propionate (Fig. 8A). Western blot analysis indicates that after siRNA-GRP43 transfection to cells for 24 h, the roles of propionate is abolished, and the protein levels of p-AKT, AKT, p-PI3K, PI3K, NLRP3, Caspase 1 and IL-18 are up-regulated (Fig. 8B and C). The protein changes of p-AKT and Caspase 1 were correlated with decreased GPR-43 in the RAW264.7 cells, which further suggest that propionate exerts an anti-inflammatory effect through GPR43 (Fig. 8D).

4. Discussion

In this study, we explore the therapeutic potential of propionate in colitis and delineated its underlying mechanism. Our

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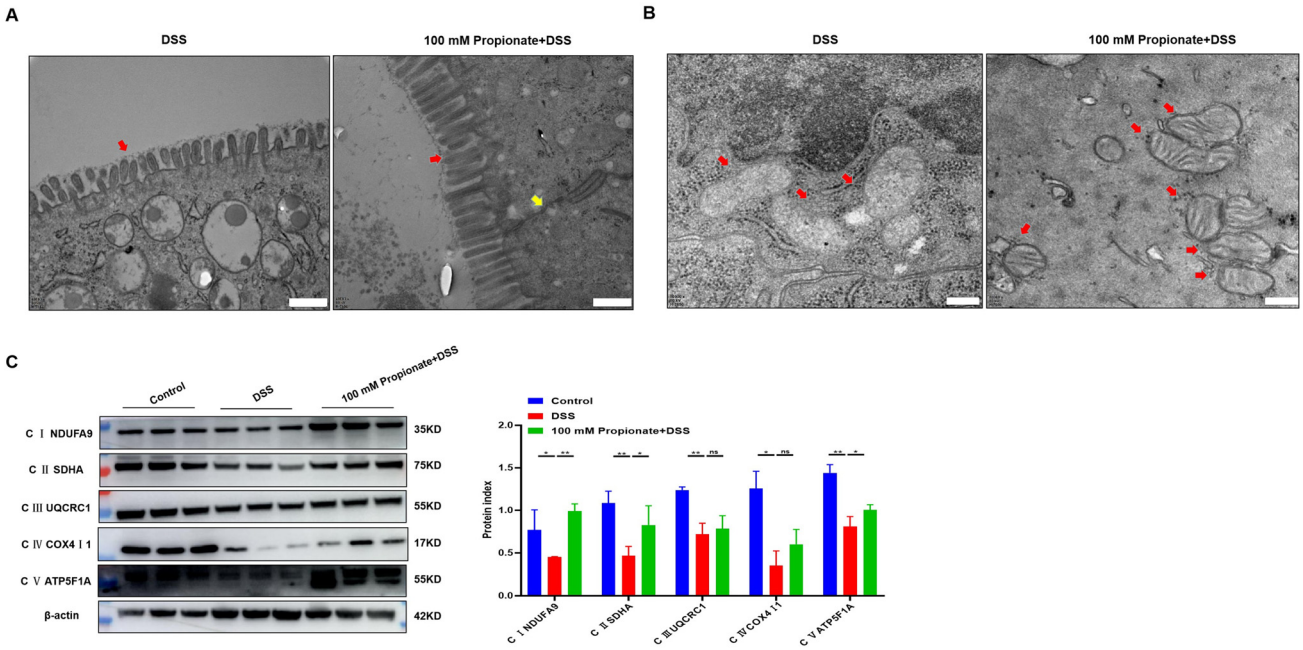

Fig. 4 Propionate attenuates DSS-induced mitochondrial dysfunction. (A) TEM images depicting the ultrastructural changes in colon epithelium and mitochondrial morphology in colon tissues. Yellow arrows indicate tight junction. Red arrows indicate colonic villi. Scale bar = 500 nm. (B) Red arrows indicate mitochondria. Scale bar = 200 nm. (C) Western blot analysis of OXPHOS protein expression in colonic tissues. Propionate treatment significantly restores the expression of respiratory complexes I, II and V (*p < 0.05, **p < 0.01; the data are presented as the mean ± SD, n = 3).

in vivo findings highlight propionate as a promising intervention to ameliorate colitis, manifested by its ability to reduce inflammatory factors, restore gut epithelial barrier integrity, and improve mitochondrial function. Notably, our investigation unveils a novel mechanism through which propionate regulates the inflammatory response by inhibiting the PI3K/AKT pathway, resulting in the downregulation of NLRP3, caspase 1, and the production of IL-1β and IL-18.

UCposes a significant global health burden, characterized by chronic inflammation of the intestinal mucosa with a complex and multifaceted etiology.[1] The dysregulated innate immune response, particularly mucosal damage resulting from aberrant immune activation, is implicated in UC pathogenesis.[36,40] The NLRP3 inflammasome, a critical component of innate immunity, has been extensively studied in the context of colitis, with studies demonstrating its pivotal role in promoting disease progression.[41] Our results align with these findings, as we observe a significant activation of the NLRP3 inflammasomes in DSS-induced colitis. This reinforces the notion that inhibiting NLRP3 inflammasome activation could be a viable therapeutic strategy for UC.[16] Our present results also confirme that the DSS significantly promotes the activation of the NLRP3 inflammasomes, thus accelerating the process of UC. So, we advocate that inhibition of NLRP3 inflammasome activation might improves UC.

Propionate, a short-chain fatty acid derived from the gut microbiota, plays a crucial role in maintaining intestinal homeostasis.[26] While the relationship between propionate and UC has been minimally explored, existing research has shown that propionate can improve intestinal barrier function, suppress inflammation, and regulate oxidative stress through the STAT3 signaling pathway, thereby alleviating UC progression.[42] Our study build upon these findings, demonstrating that propionate effectively ameliorates key symptoms of UC, including weight loss, shortened colon length and increased DAI score. Furthermore, propionate reduces inflammatory cytokine expression and restores the gut epithelial barrier, underscoring its potential therapeutic efficacy in UC.

Mitochondrial dysfunction is a recognized feature of UC, contributing to disease onset and recurrence.[43,44] Mitochondrial dysfunction and intestinal mucosal energy deficiency has also been reported in UC patients and DSS mice.[45] Mitochondrial dysfunction may contribute to reduced ATP production, increased levels of ROS and oxidative stress, affecting the normal function of the cells and the repair ability of the intestinal mucosa.[46] Mitochondrial dysfunction promotes the abnormal activation of the immune system, causing the impairment of the intestinal mucosal barrier, leading to the development of inflammatory intestinal disease (IBD), and accelerating the progression of inflammation.[47] Mitochondrial dysfunction may be closely related to the development of IBD by affecting the integrity of the intestinal barrier, triggering immune responses, and then affecting the composition and function of the intestinal flora.[48] Mitochondria play a key role in the regulation of cell death, and mitochondrial dysfunction may lead to increased apoptosis and necrosis, affecting intestinal cell homeostasis and repair.[49] Therefore, the maintenance of mitochondrial homeostasis is essential for intestinal health.

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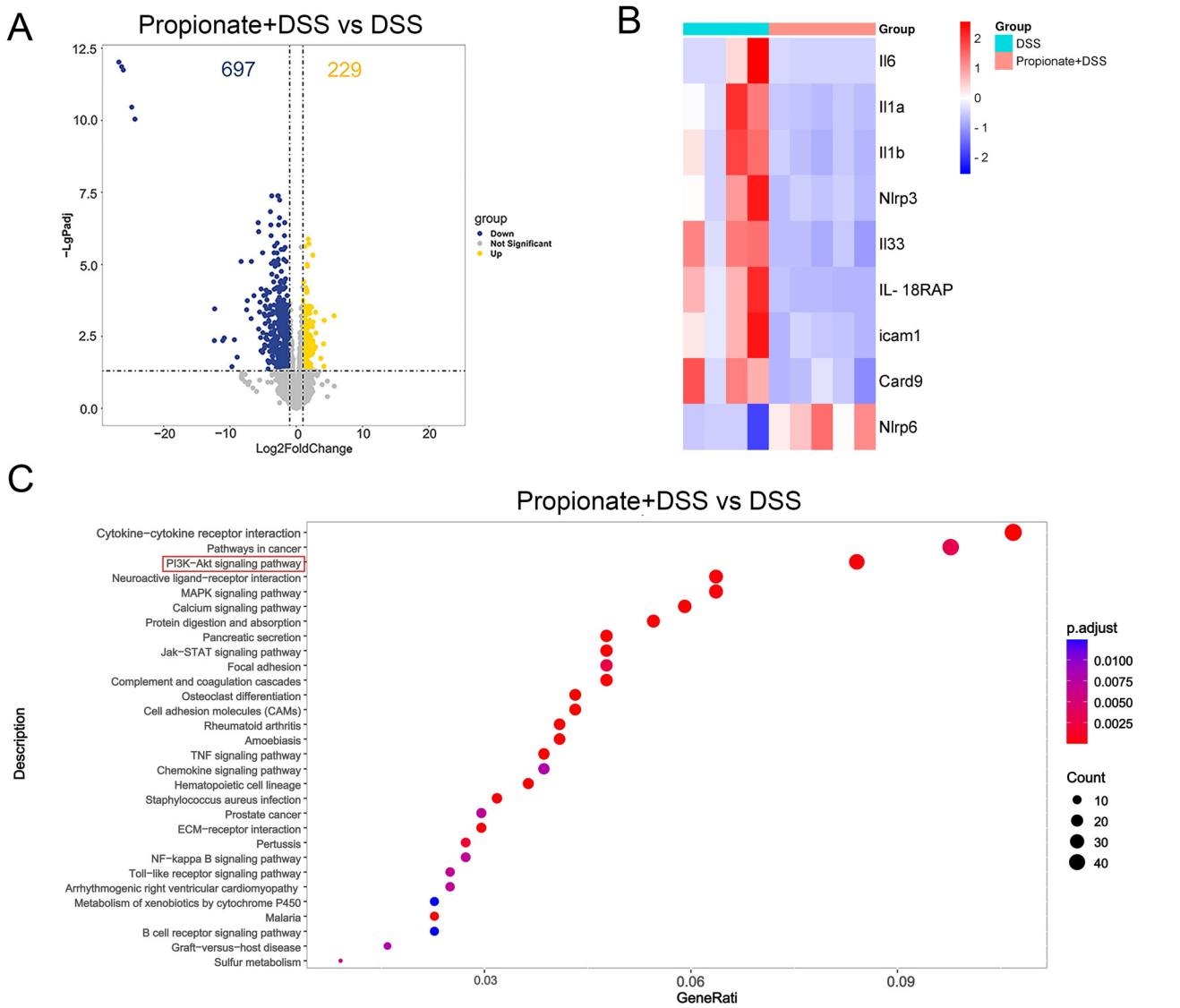

Fig. 5 Differential genes are analyzed by transcriptome sequencing. (A) Volcano plot showing statistical significance (−log10) against log2 fold change between propionate + DSS and DSS groups. Genes statistically significant (fold change >2, $p < 0.05$) are annotated. (B) Heatmap of distinctly dysregulates mRNAs in mice (propionate + DSS *vs.* DSS) identify from transcriptome sequencing by hierarchical clustering. Different colors represent the high and low expression of the genes. (C) Enriched pathways are identified by transcriptome sequencing in mice. The different colors represent the statistical differences, the size of the circle expresses the number of genes in each pathway.

Our results corroborate these findings, illustrating disrupted mitochondrial structure and function in DSS-induced colitis in mice. However, propionate treatment remarkably improves mitochondrial morphology and function, emphasizing its protective role against UC-associated mitochondrial impairments. This aligns with previous studies demonstrating the beneficial effects of propionate in mitigating mitochondrial dysfunction in various contexts.[50]

Mitochondria play a key role in the activation and regulation of the NLRP3 inflammasome.[51] Mitochondria are responsible for energy generation, calcium signaling, and apoptosis, and they are the main source of reactive oxygen species. Mitochondrial dysfunction can lead to the release of damage-associated molecular patterns (DAMPs), which can activate inflammasomes and trigger an inflammatory response.[52–54] The generation of mitochondrial reactive oxygen species (mtROS), which arises from mitochondrial dysfunction and electron transport system failure, can enhance the activation of the NLRP3 inflammasome. The accumulation of mtROS can lead to mitochondrial DNA damage, which in turn triggers the activation of the inflammasome due to increased mitochondrial dysfunction, ATP depletion, and intrinsic apoptosis.[55] The increase in mitochondrial DNA (mtDNA) resulting from mitochondrial abnormalities triggers the NLRP3 inflammasome *via* the cGAS-STING pathway, thereby promoting the progression of inflammatory diseases.[52,56,57] ATP can promote

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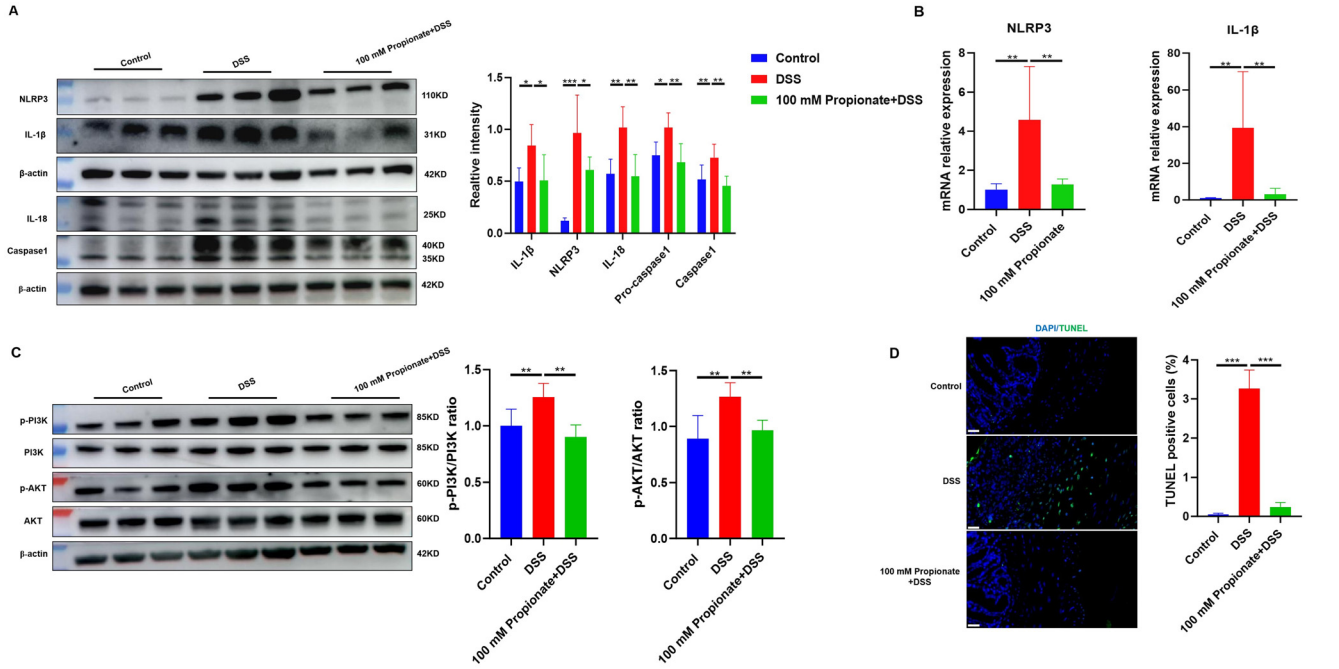

Fig. 6 Propionate improves DSS-induced colitis by inhibiting PI3K/AKT signaling pathway and relieving the NLRP3 inflammasome activation. (A) NLRP3, Pro-caspase 1, Caspase 1, IL-1β and IL-18 proteins of colon tissues in mice are assessed by western blot (n = 6). (B) mRNA levels of NLRP3 and IL-1β in mice colon tissues are assessed by qPCR (n = 6). (C) Protein levels of PI3K, p-PI3K, AKT and p-AKT in colon tissues from mice are determined by western blot analysis (n = 6). (D) TUNEL staining in colon sections from treated mice. Representative images and quantification of TUNEL positive cells. Scale bar = 20 μm (n = 3) (*p < 0.05, **p < 0.01, ***p < 0.001; the data are the mean ± SD).

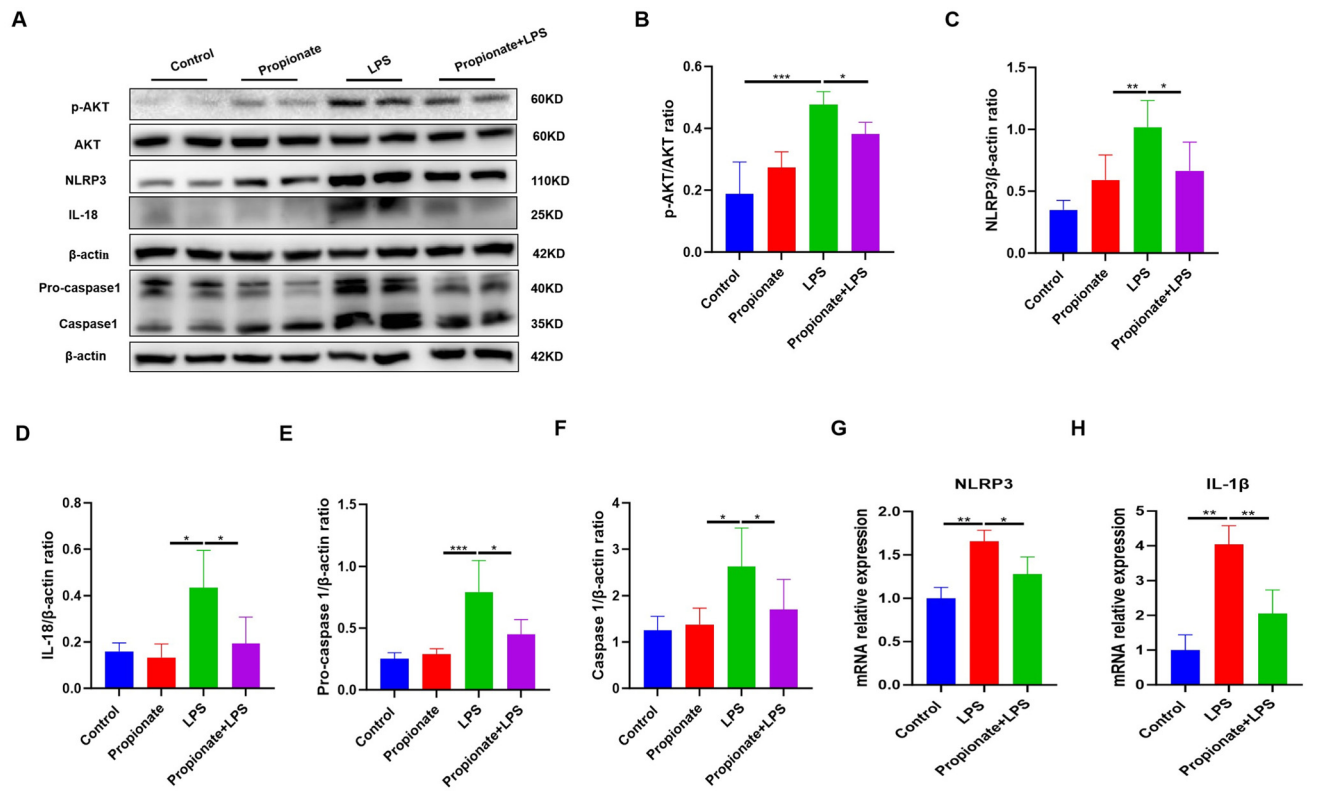

Fig. 7 Propionate acts by inhibiting the PI3K/AKT signaling pathway and the activation of the NLRP3 inflammasome in RAW264.7 cells. RAW264.7 cells are treated by LPS for 6–8 h with or without propionate (0.3 mM, 2 h). (A–F) Protein levels of AKT, p-AKT, NLRP3, IL-18, Pro-caspase 1 and Caspase 1 are assessed by western blot analysis (n = 3–5). (G and H) Transcriptional levels of NLRP3 and IL-1β are detected by qPCR (n = 3) (*p < 0.05, **p < 0.01, ***p < 0.001; the data are the mean ± SD).

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the accumulation of α-synuclein, which in turn activates the NLRP3 inflammasome, triggering the inflammatory response.[58] Our transcriptome sequencing, followed by validation through western blotting and qPCR, reveals that propionate effectively inhibits NLRP3 inflammasome activation, resulting in reduced production of IL-1β and IL-18. The intricate crosstalk between mitochondrial function, the NLRP3 inflammasome, and UC pathogenesis is further supported by the literature.[17,51] Collectively, our findings suggest that propionate's mitigation of UC involves the restoration of mitochondrial function and subsequent inhibition of NLRP3 inflammasome activation.

UC patients also exhibit mitochondrial dysfunction and an abnormal accumulation of mitochondria. Mitochondrial autophagy, a process essential for maintaining cell health by eliminating damaged mitochondria, is critical. Dysfunction in mitochondrial autophagy can result in abnormal mitochondrial accumulation and heightened inflammatory responses, thereby furthering the progression of UC. Mitochondrial autophagy diminishes mtROS and oxidative stress by selectively

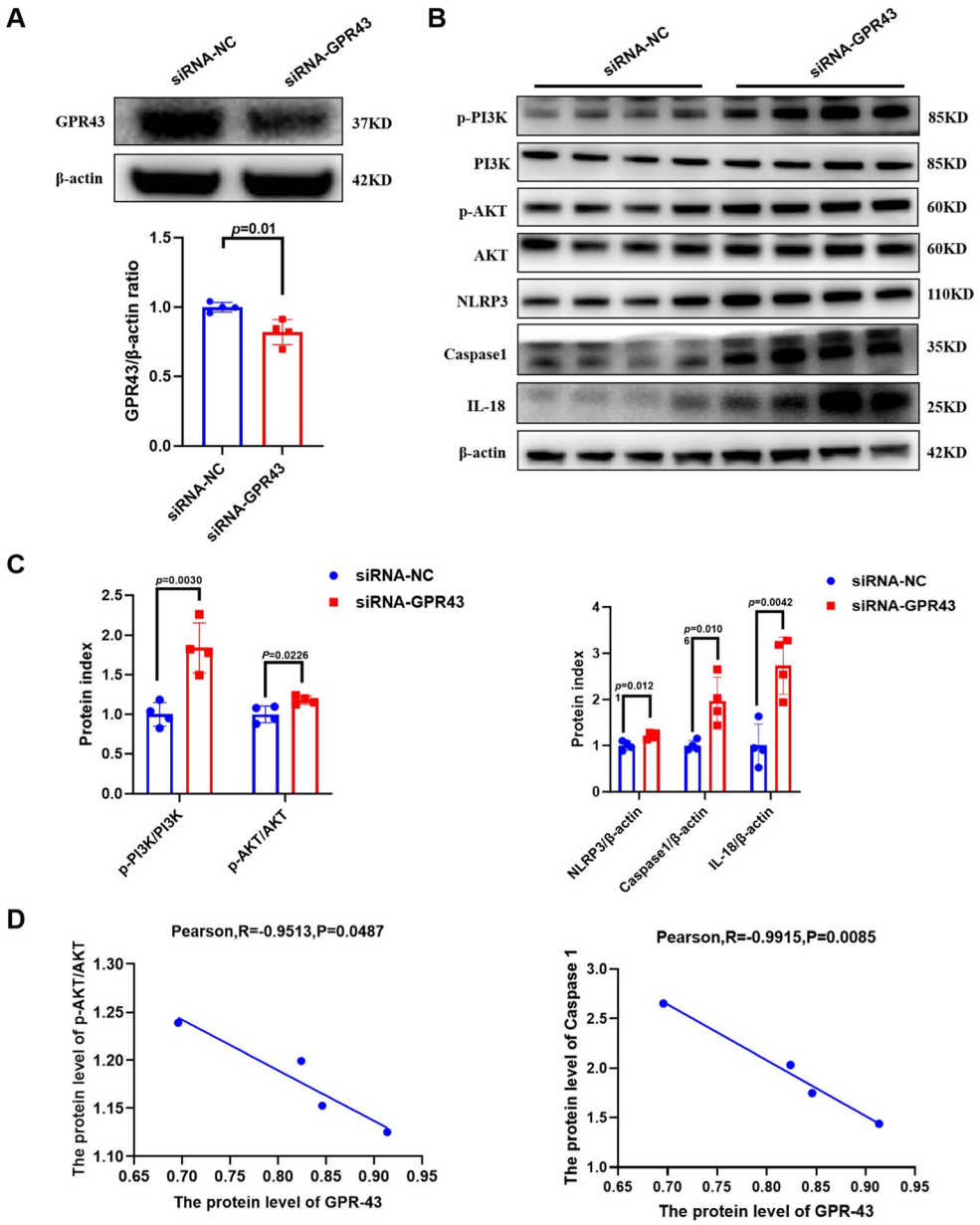

Fig. 8 Propionate inhibits the AKT signaling pathway and the activation of NLRP3 inflammasome through its receptor, GPR43. (A) The knockdown efficiency of siRNA is verified by western blot. (B and C) RAW264.7 cells are stimulated with LPS for 6–8 h in the presence of propionate (0.3 mM) after transfection. Western blot analysis assesses the levels of AKT, p-AKT, p-PI3K, PI3K, NLRP3, IL-18 and Caspase 1. (D) Association of altered PI3K/AKT pathway, Caspase 1 and decreased aggregation of GPR-43 in the RAW264.7 cells in longitudinal studies (*$p < 0.05$, **$p < 0.01$; the data are the mean ± SD, $n = 4$).

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breaking down damaged or dysfunctional mitochondria, thereby reducing the inflammatory response of the intestinal mucosa.[59] Mitochondrial autophagy also suppresses the overactivation of the NLRP3 inflammasome and mitigates intestinal inflammation by eliminating damaged mitochondria, thereby reducing the release of mtDNA and the accumulation of mtROS.[60] Studies have reported that propionate enhances PINK1/PARKIN-mediated mitochondrial autophagy *via* GPR43, thereby maintaining mitochondrial homeostasis.[61] Therefore, in light of our findings, propionate treatment significantly improved mitochondrial morphology and function. Moreover, we also found that inhibiting GPR43 negated the anti-inflammatory effects of propionate. Thus, we speculate that propionate enhances mitochondrial autophagy *via* GPR43, maintains mitochondrial homeostasis, and improves the intestinal inflammatory response. However, the roles of propionate in maintaining mitochondrial autophagy and function in UC mice still require further in-depth research in the future.

The PI3K/AKT signaling pathway has been implicated in the regulation of NLRP3 inflammasome activation,[62–64] with AKT as the main effector regulating many cell functions.[65] The priming signal through PI3K/AKT can activate IkB kinase and promote the activation of NF-kB pathway to induce IL-1β.[66] Our transcriptome sequencing reveals an enrichment of the PI3K/AKT signaling pathway upon propionate treatment, prompting us to investigate its role in DSS-induced colitis. Western blot analysis confirmes an upregulation of the PI3K/AKT pathway in DSS-induced mice, which is significantly reduced by propionate treatment. LY294002, an inhibitor of PI3K/AKT signaling pathway, improves intestinal symptoms in DSS-induced mice, the dual effect of propionate and LY294002 are more effective. It was reported that glycyrrhetinic acid relieved acute lung injury *via* inhibiting the PI3K/AKT signaling pathway and subsequently inhibiting the activation of the NLRP3 inflammasome.[67] *In vitro* experiments further support these findings, with propionate inhibiting LPS-induced upregulation of p-AKT, NLRP3, IL-18, Pro-caspase 1 and Caspase 1. The use of SC79, an AKT agonist, corroborates the role of PI3K/AKT signaling pathway in NLRP3 inflammasome activation. These results collectively indicate that propionate exerts its anti-inflammatory effects by inhibiting NLRP3 inflammasome activation through the modulation of the PI3K/AKT signaling pathway. GPR43 is a receptor for propionate, in mediating its anti-inflammatory effects, which is consistent with our observations where siRNA-mediated knockdown of GPR43 results in abrogating propionate's anti-inflammatory actions and levels PI3K, AKT, NLRP3 and related proteins.

5. Conclusion

In summary, our study unveils a multifaceted mechanism through which propionate mitigates UC, involving the restoration of mitochondrial function, inhibition of the NLRP3 inflammasome, and modulation of the PI3K/AKT signaling pathway. These findings not only contribute to our understanding of UC pathogenesis but also provide a rationale for exploring propionate as a therapeutic avenue in UC management.

Author contributions

Yao Shi: Data curation, formal analysis, investigation, visualization, software, writing – original draft. Danqing Xin: Data curation, investigation, formal analysis. Haojie Zhang: Performed animal models. Shuanglian Wang: manuscript proof reading and editing. Maojun Yang and Chuanyong Liu: Conceptualization, funding acquisition, resources, project administration, writing – review & editing.

Conflicts of interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

We performed animal experiments on the basis of the International Guiding Principle for Animal Research that was stipulated by the Council for International Organizations of Medical Sciences (CIOMS). The approach in this study was approved by the Tsinghua University and Shandong First Medical University & Shandong Academy of Medical Sciences Animal Ethics Committee. The participants in the animal models received formal training according to the rules of the Institutional Animal Care and Use Committee Guidebook (IACUC). Written informed consent was obtained from all authors.

Abbreviations

DAPI	4′,6′Diamidino-2-phenylindole dihydrochloride hydrate
DMEM	Dulbec's modified Eagle's medium
DSS	Dextran sulfate sodium;
FBS	Fetal bovine serum
IBD	Inflammatory bowel disease
IL	Interleukin
LPS	Lipopolysaccharide
NLR	Nucleotide-binding domain and leucine-rich repeat-containing
PI3K	Phosphatidylinositol 3-kinase
qPCR	Reverse transcriptase quantitative real-time PCR
SCFAs	Short-chain fatty acids
TGF-β	Transforming growth factor β
TNF-α	Tumor necrosis factor-α
UC	Ulcerative colitis

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Data availability

The data during our research cannot be publicly available due to the data safety concern. But the data are available from the corresponding author on reasonable request.

Acknowledgements

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