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Akkermansia muciniphila ameliorates inflammatory bowel disease by modulating gut tight junctions in mice

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Inflammatory bowel disease (IBD) affects more than 300,000 UK citizens and incidence of IBD has almost doubled among young people (aged 10–16) between 2000 and 2018. In IBD, the intestinal epithelium is weakened, increasing permeability to microbial toxins and faecal waste, perpetuating chronic inflammation in the digestive tract[1,2]. IBD is intrinsically linked to nutritional imbalance and dysbiosis of the gut microbiome; research demonstrates that abundance of commensal gut bacterium *Akkermansia muciniphila* (*A. muciniphila*) is associated with development of metabolic diseases including IBD[3]. In this study, we aim to identify the underlying mechanism of *A. muciniphila* in ameliorating gut inflammation and improving gut integrity in IBD induced by dextran sodium sulphate (DSS).

C57/B6 mice were treated by oral gavage with either 200 µL 109 CFU/mL *A. muciniphila* or 200 µL PBS every 2 days over a period of 2 weeks (n = 5-6/group). Additionally, the mice were supplied with drinking water containing 1.5% DSS to induce IBD; plasma, ileum, and colon tissue were harvested at the end of treatment for further analysis of gene expression by immunoblotting analysis and quantitative polymerase chain reaction (q-RT-PCR). Protein signal intensity in the immunoblotting analysis was quantified using the software ImageJ and hypotheses tests of statistical significance ($P < 0.05$) on quantified data conducted by two-tailed homoscedastic t-test.

Our study showed that DSS treatment induced inflammatory bowel disease (IBD), indicating by the increased expression of inflammatory cytokine genes, IL-1β, IL-6 and TNFα, in colon tissue (Figure 1A, $p < 0.05$). Metabolic analysis further revealed significantly higher level of homocysteine in the blood, suggesting the concomitant induction of systemic inflammation in the IBD mice ($p < 0.05$). Mechanistic study showed that DSS treatment activated the ER stress markers, eIF2a and JNK, in the intestinal epithelial cells. q-RT-PCR and immunoblotting analysis further revealed upregulated expression of claudin-2 but downregulated claudin-1, claudin-3, occludin and ZO-1 ($p < 0.05$). Claudin-2 is expressed at leaky epithelia to form water permeable paracellular channels[4] whereas claudin-1, claudin-3, occludin and ZO-1 are gut tight junctions that form the gut barrier. Changes of the expression of these gut tight-junction proteins contributed to the development of IBD. Importantly, *A. muciniphila* treatment ameliorated intestinal inflammation and epithelial cell stress which were associated with the inhibition of claudin-2 expression and improvement of gut integrity (Figure 1B, $p < 0.05$).

In conclusion, increased colonization of *A. muciniphila* in the gut *improved IBD by modulating gut tight-junction expression, inhibiting ER stress and inflammation in the intestinal epithelium.*

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