Protectin D1 Induced by *Clostridium butyricum* MIYAIRI 588 Has Anti-inflammatory Effects on Antibiotic-induced Intestinal Disorder

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Introduction

Metabolites are thought as the end products in regulation of cellular processes and their levels show the strongest relationships with the phenotype. Previously, we showed that the administration of *Clostridium butyricum* MIYAIRI 588 (CBM 588) upregulated protectin D1, an anti-inflammatory lipid metabolite, in colon tissue under antibiotic treatment. However, how CBM 588 induces protectin D1 expression and whether the lipid metabolites induced by CBM588 has anti-inflammatory effects on antibiotic-induced inflammation are unclear. Therefore, here, we evaluated the effect of CBM 588 on lipid metabolism and protectin D1 in gut protection from antibiotic-induced intestinal disorders.

Materials/methods

Mice were divided into five groups and clindamycin (CLDM), CBM 588 and/or protectin D1 were administered for 4 days (1. Control, 2. CLDM group, 3. CBM 588 group, 4. CLDM plus CBM 588 group and 5. CLDM plus protectin D1 group). After 4 days of administration, mice were reared for an additional 4 days. On day 8, colon tissues were removed to measure lipid metabolites with LC-MS/MS. Also, cytokines, lipid metabolism-relative genes and proteins were measured with RT-PCR or ELISA.

Results

Figure 1: The lipid metabolites in colon tissue were analyzed by LC-MS/MS. The MS signal intensities of α-linolenic acid, eicosapentaenoic acid (EPA), 15-hydroxy docosahexaenoic acid (HDoHE) and protectin D1 were significantly increased in the CBM588 treatment group.

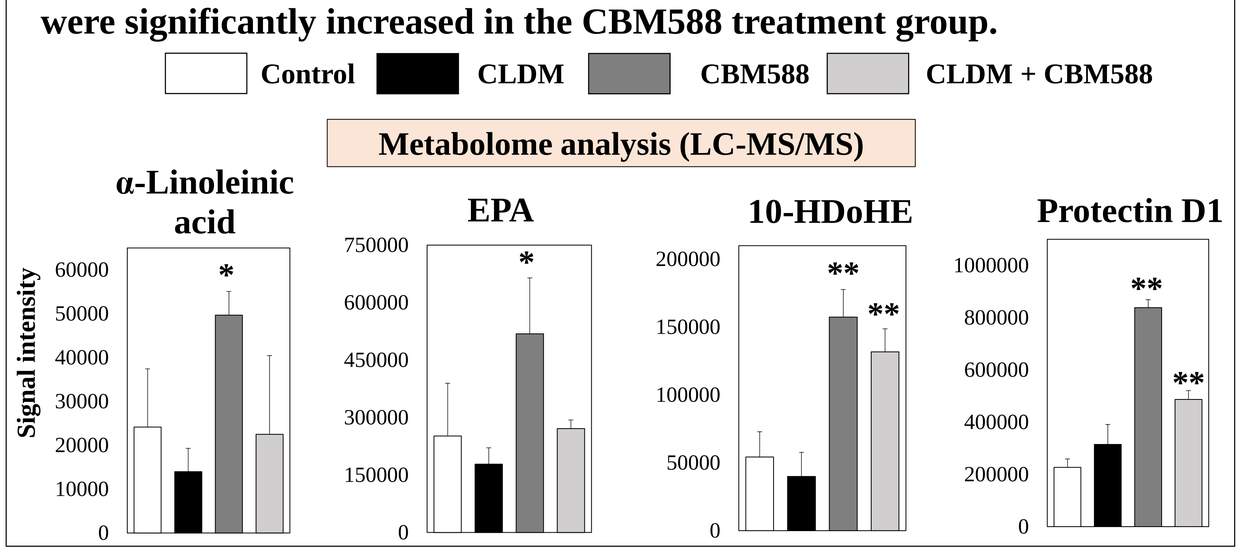
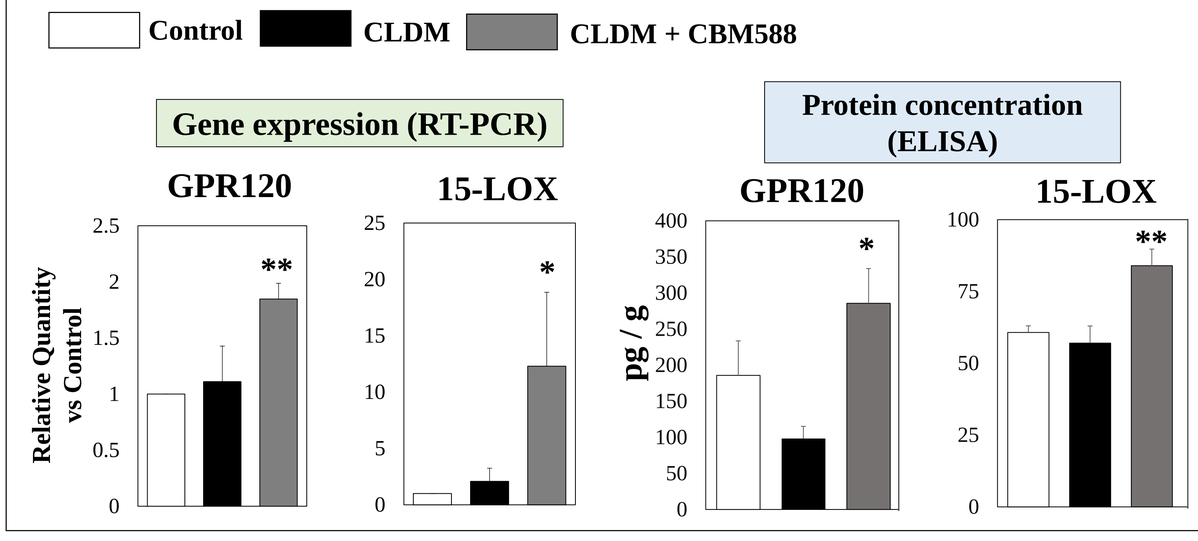


Figure 2: Genes expression levels and protein concentration of GPR120 (a poly-unsaturated fatty acids receptor) and 15-LOX (a lipoxygenase, catalyzing enzyme from docosahexaenoic acid to protectin D1) were increased in the colon tissue of CBM588 treated group.



*: $p < 0.05$ compared with control. **: $p < 0.01$ compared with control

Figure 3: In mice colon, concentration of IL-4, which is speculated to be produced by Th2 cells, was increased in the CBM588 treatment group.

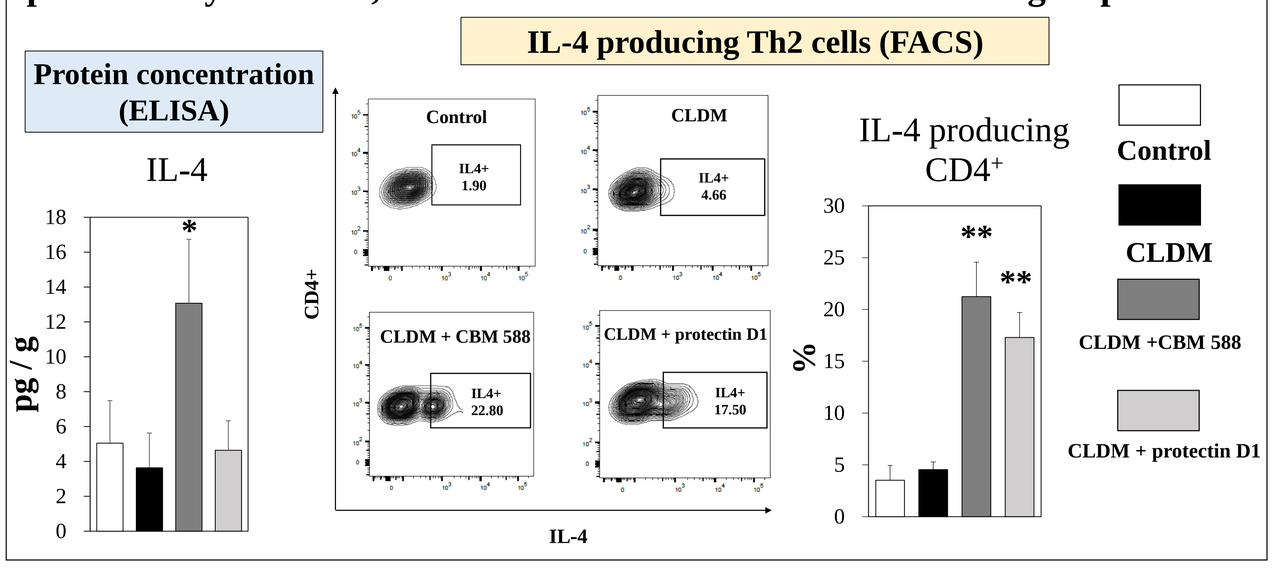
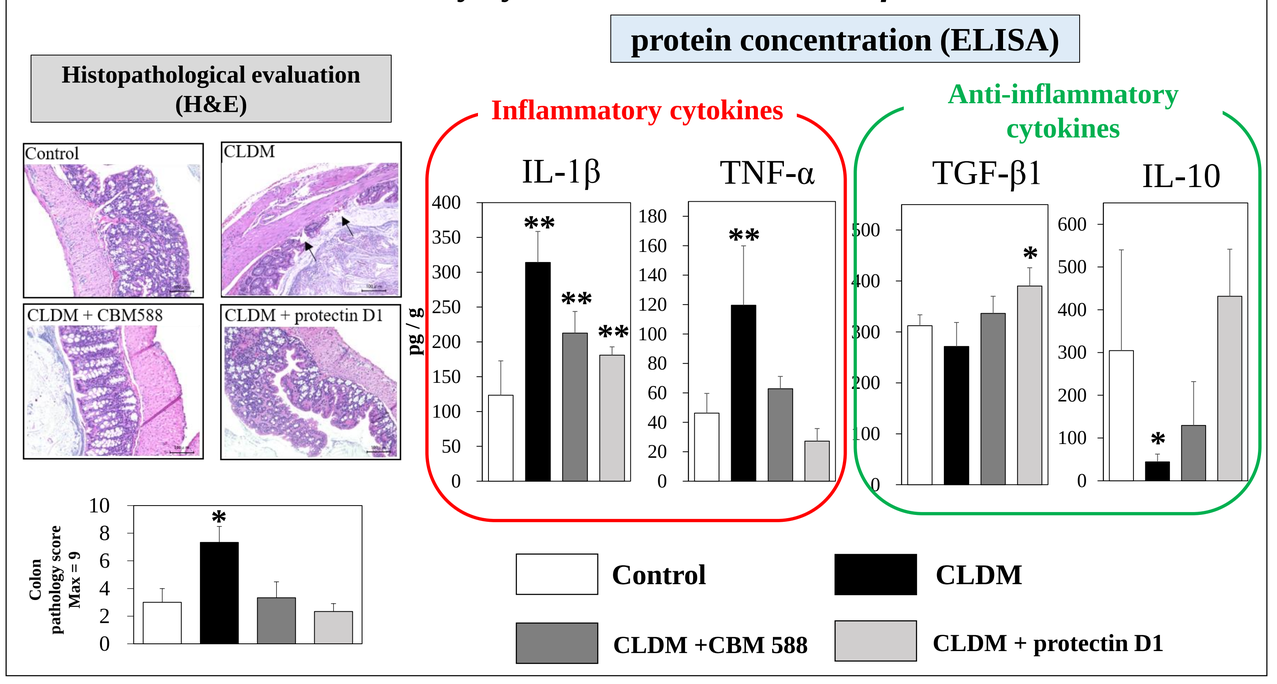
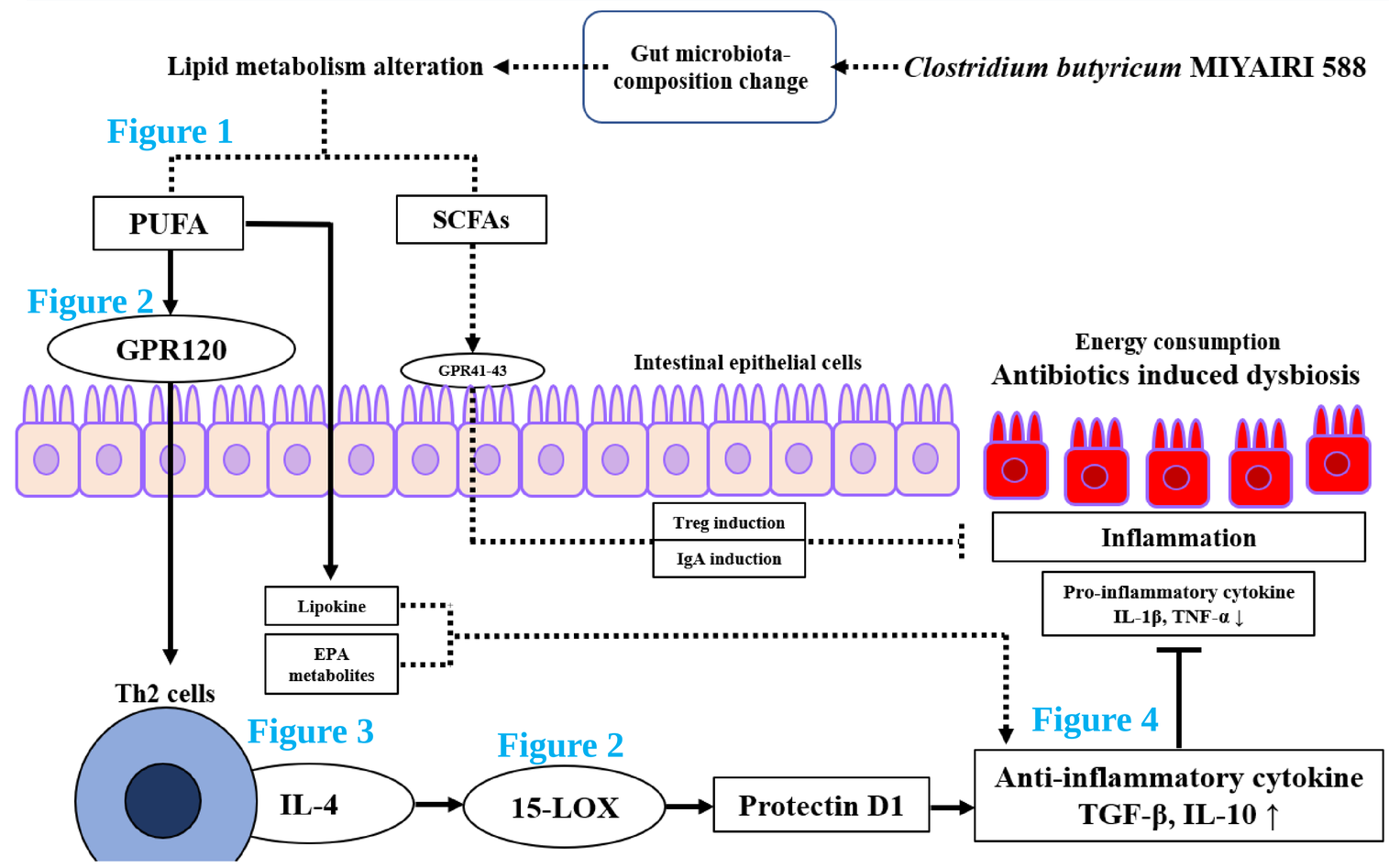


Figure 4: Similar to CBM 588 administration, protectin D1 administration suppressed mice's gut inflammation, decreased inflammatory cytokines, while increased anti-inflammatory cytokine IL-10 and TGF-β1.



Conclusions



Our data revealed that CBM 588 activated 15-LOX to enhance protectin D1 production by increasing IL-4-producing $CD4^+$ cell population in the intestinal tract. Additionally, CBM 588-induced protectin D1 clearly upregulated IL-10-producing $CD4^+$ cells to control antibiotic-induced gut inflammation. We provide new insights into CBM 588-mediated lipid metabolism induction for the treatment of gut inflammatory diseases.

Acknowledgements

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