

## The gut microbiota shapes intestinal immune responses during health and disease

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In the version of this article initially published, references for table 2 were missing. A referenced version is provided below.

Table 2 | Bacteria shown to be protective in inflammatory bowel disease

Bacterial strain	Model system	Disease type or model	Mechanism of disease suppression	Refs
VSL#3*	Human and mouse	Pouchitis, ulcerative colitis and TNBS-induced colitis	Induction of IL-10- and TGF $\beta$ -expressing T cells	1–3
<i>Bifidobacteria lactis</i>	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS	4
<i>Bifidobacteria infantis</i>	Mouse	<i>Salmonella enterica</i> -induced enteritis	Induction of T <sub>Reg</sub> cells and inhibition of NF- $\kappa$ B activation	5
<i>Escherichia coli</i> Nissle 1917	Human and mouse	Ulcerative colitis and DSS-induced colitis	Decreased colonic inflammation induced by TLR2 and TLR4 activation	6,7
<i>Lactobacillus rhamnosus</i> GG	Mouse and rat	TNBS-induced colitis and HLA-B27-associated colitis	Induction of T <sub>Reg</sub> cells	8,9
<i>Lactobacillus salivarius</i>	Mouse	TNBS-induced colitis	Decreased colonic inflammation	8
<i>Lactobacillus reuteri</i>	Mouse	IL-10-deficient mice	Upregulation of NGF and decreased levels of IL-8 and TNF in cell lines	10,11
<i>Lactobacillus plantarum</i> 299v	Mouse	IL-10-deficient mice	Decreased levels of IFN $\gamma$ and IL-12p40	12
<i>Lactobacillus fermentum</i>	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS	13
<i>Lactobacillus casei</i>	Rat	TNBS-induced colitis	Decreased levels of colonic cyclooxygenase 2	4
<i>Bacteriodes thetaiotaomicron</i>	Rat	<i>S. enterica</i> -induced enteritis	Decreased levels of IL-8 and TNF in colorectal adenocarcinoma cell line	14
<i>Bacteriodes fragilis</i>	Mouse	T cell transfer and TNBS-induced colitis	Production of CD4 <sup>+</sup> T cell-derived IL-10	15
YO-MIX Y109 FRO 1000 <sup>†</sup>	Mouse	TNBS-induced colitis	ND	9
<i>Faecalibacterium prausnitzii</i>	Mouse	TNBS-induced colitis	Decreased levels of NF- $\kappa$ B, IL-8 and TNF and increased IL-10 production	16

\*A mixture of *Lactobacillus* spp. (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Lactobacillus delbrueckii* subspecies *bulgaricus*), *Bifidobacterium* spp. (*Bifidobacterium longum*, *Bifidobacterium breve* and *Bifidobacterium infantis*) and *Streptococcus salivarius* subspecies *thermophilus*. <sup>†</sup>A mixture of *S. thermophilus*, *L. acidophilus* and *B. longum*. DSS, dextran sulphate sodium; IFN $\gamma$ , interferon- $\gamma$ ; IL, interleukin; iNOS, inducible nitric oxide synthase; ND, not determined; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NGF, nerve growth factor; TGF $\beta$ , transforming growth factor- $\beta$ ; TLR, Toll-like receptor; TNBS, trinitrobenzene sulphonic acid; TNF, tumour necrosis factor; T<sub>Reg</sub>, regulatory T.

- Mimura, T. *et al.* Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* **53**, 108–114 (2004).
- Bibiloni, R. *et al.* VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am. J. Gastroenterol.* **100**, 1539–1546 (2005).
- Di Giacinto, C., Marinaro, M., Sanchez, M., Strober, W. & Boirivant, M. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF- $\beta$ -bearing regulatory cells. *J. Immunol.* **174**, 3237–3246 (2005).
- Peran, L. *et al.* A comparative study of the preventative effects exerted by three probiotics, *Bifidobacterium lactis*, *Lactobacillus casei* and *Lactobacillus acidophilus*, in the TNBS model of rat colitis. *J. Appl. Microbiol.* **103**, 836–844 (2007).
- O'Mahony, C. *et al.* Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF- $\kappa$ B activation. *PLoS Pathog.* **4**, e1000112 (2008).
- Kruis, W. *et al.* Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut* **53**, 1617–1623 (2004).
- Grabig, A. *et al.* *Escherichia coli* strain Nissle 1917 ameliorates experimental colitis via Toll-like receptor 2- and Toll-like receptor 4-dependent pathways. *Infect. Immun.* **74**, 4075–4082 (2006).
- Foligne, B. *et al.* Correlation between *in vitro* and *in vivo* immunomodulatory properties of lactic acid bacteria. *World J. Gastroenterol.* **13**, 236–243 (2007).
- Amit-Romach, E., Uni, Z. & Reifen, R. Therapeutic potential of two probiotics in inflammatory bowel disease as observed in the trinitrobenzene sulfonic acid model of colitis. *Dis. Colon Rectum* **51**, 1828–1836 (2008).
- Madsen, K. L., Doyle, J. S., Jewell, L. D., Tavernini, M. M. & Fedorak, R. N. *Lactobacillus* species prevents colitis in interleukin 10 gene-deficient mice. *Gastroenterology* **116**, 1107–1114 (1999).
- Ma, D., Forsythe, P. & Bienenstock, J. Live *Lactobacillus reuteri* is essential for the inhibitory effect on tumor necrosis factor  $\alpha$ -induced interleukin-8 expression. *Infect. Immun.* **72**, 5308–5314 (2004).
- Schultz, M. *et al.* *Lactobacillus plantarum* 299V in the treatment and prevention of spontaneous colitis in interleukin-10-deficient mice. *Inflamm. Bowel Dis.* **8**, 71–80 (2002).
- Peran, L. *et al.* A comparative study of the preventative effects exerted by two probiotics, *Lactobacillus reuteri* and *Lactobacillus fermentum*, in the trinitrobenzenesulfonic acid model of rat colitis. *Br. J. Nutr.* **97**, 96–103 (2007).
- Kelly, D. *et al.* Commensal anaerobic gut bacteria attenuate inflammation by regulating nuclear-cytoplasmic shuttling of PPAR- $\gamma$  and RelA. *Nature Immunol.* **5**, 104–112 (2004).
- Mazmanian, S. K., Round, J. L. & Kasper, D. L. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* **453**, 620–625 (2008).
- Sokol, H. *et al.* *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc. Natl. Acad. Sci. USA* **105**, 16731–16736 (2008).