Table S1. Examples of how gut bacteria exert a pro- or anti-inflammatory impact

Bacterial species	Known mechanisms
BACTERIA WITH AN ALLEVIATING IMPACT	
Firmicutes	
Faecalibacterium prausnitzii[1-3]	Butyrate production, induction of regulatory T cells, energy supply to intestinal epithelium
Roseburia spp. *[1, 4]*	Butyrate production
Clostridium clusters IV and XIVa[5]	Butyrate production
Dialister invisus. [2, 5]	Acetate/proprionate production
Ruminococcus spp. *[6-9]*	Butyrate production, Mucus degradation
Bacteroidetes	
Bacteroides fragilis[10, 11]	Induction of IL-10 production from regulatory T cells, suppression of IL-17 production
Actinobacteria	
Bifidobacterium spp.*[5, 12]*	Acetate/proprionate production, induction of IL-10 production from regulatory T cells
Verrucomicrobia	
Akkermansia muciniphila[7]	Acetate/proprionate production, mucus changes
Proteobacteria	
Helicobacter pylori[13]	Induction of tolerogenic dendritic and regulatory T cells
BACTERIA WITH AN ENHANCING IMPACT	
Bacteroidetes	
Prevotella spp.*[14]*	Hampers acetate production
Bacteroides spp. *[15]*	Cleavage of junctional protein, induction of epithelial-derived IL-8, epithelial invasion
Proteobacteria	
Escherichia coli[1, 16]	Adhesion and invasion of colon epithelium, LPS release at cell death
Shigella spp.*[1, 16]*	Adhesion and invasion of colon epithelium, LPS release at cell death
Fusobacteria	
Fusobacterium spp. *[17]*	Adhesion and invasion of colon epithelium, induction of epithelial-derived IL-8 and TNF-α

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Table S2. Inflammatory bowel disease–associated genes involved in gut barrier immunology and microbiome handling

Gene Symbol	Genomic location*	Gene name	CD/UC/ IBD/ VEO-IBD	Genes in GWAS region	Intestinal epithelial cell expression (proteinatlas) (first cell type=most expressed)	Known function in epithelial cells	Coding variant**	REFs
ALPI	chr2:232,456,125-232,460,753	Alkaline phosphatase, intestinal	VEO-IBD		Proximal enterocytes (enriched), distal enterocytes, paneth cells, intestinal goblet cells	Regulates the response to LPS[1]. Regulates tight junction, lyzozyme secretion, autophagy and mucus secretion[2].	ALPI(A360V), ALPI(Q439X)	[3]
ATG16L1	chr2:233,210,051-233,295,674	Autophagy related 16 like 1	CD	INPP5D, ATG16L1,SAG	Distal enterocytes, proximal enterocytes, paneth cells, intestinal goblet cells	Regulates the Paneth cell granule exocytosis pathway[4]. Regulates Paneth cell endoplasmic reticulum stress[5]. Regulates autophagy[6].	ATG16L1(T300A)	[7], [8]
IFIH1	chr2:162,267,074-162,318,684	Interferon induced with helicase C domain 1	UC	FAP,IFIH1	Proximal enterocytes, intestinal goblet cells, distal enterocytes, paneth cells	Implicated in the response to viruses[9].	IFIH1(I923V)	[10], [8]
NOD2	chr16:50,693,588-50,734,041	Nucleotide binding oligomerization domain containing 2	CD	CYLD,NOD2,SNX20	Expressed in Caco-2 cells	Regulates anti-microbial peptide secretion in Paneth cells[11]. Regulates autophagy[12]. Regulates crypt survival[13]. Regulates ROS production[14]. Regulates mucus production by goblet cells[15]. Regulates the recognition of intestinal microflora[15]. Regulates apoptosis[16]. Regulates cell proliferation[15]. Regulates the response to endoplasmic reticulum stress[17].	NOD2(R702W), NOD2(V793M), NOD2(S431L), NOD2(N289S), NOD2(N852S), NOD2(N872S), NOD2(fs1007insC), NOD2(G908R)	[18], [19], [8]
ADAM17	chr2:9,488,486-9,556,732	ADAM metallopeptidase domain 17	VEO-IBD		Distal enterocytes, paneth cells, intestinal goblet cells, proximal enterocytes	Modulates the response to TNF-α and EGFR[20]. Regulates tight junctions and cell shedding[21]. Regulates apoptosis in mouse[22]. Regulates mucus production in mouse[23]. Regulates cell proliferation[23].	ADAM17 (p.Val673Ile)	[24], [25]
TTC7A	chr2:46,916,157-47,076,137	Tetratricopeptide repeat protein 7A	VEO-IBD		Proximal enterocytes, distal enterocytes, paneth cells, intestinal goblet cells	Binds to PI4KIIIalpha and recruits it to the plasma membrane to produce PI4P[26],[27]. PI4P is implicated in cell polarization and cell survival[28].	E71K, A832T, and Q526X	[27]

C1orf106	chr1:200,891,048-200,915,742	Innate immunity activator	IBD	CAMSAP2,KIF21B,GPR25,CACNA1S,C1orf106	Expressed in Caco-2 cells	Regulates epithelial permeability through the regulation of adherens junction stability[29]. Regulates IL-1B signal transduction[30].	C1orf106(p.Y333F)	[31], [29]
FUT2	chr19:48,695,971-48,705,951	Fucosyltransferase 2	CD	NTN5,RASIP1,FUT2,MAMSTR,FUT1,IZUMO1	Proximal enterocytes (enriched), distal enterocytes (enriched), paneth cells (enriched), intestinal goblet cells	Intestinal epithelial cell fucosylation[32].	FUT2(W154X), FUT2(G258S)	[33-36], [8]
RNF186	chr1:19,814,029-19,815,283	Ring finger protein 186	UC	OTUD3, RNF186, TMCO4	Paneth cells (enriched), intestinal goblet cells (enriched), distal enterocytes (enriched), proximal enterocytes	E3 ubiquitin-protein ligase that regulates autophagy[37]. Regulates cell proliferation and migration[38]. Regulates endoplasmic reticulum stress[39].	RNF186(R179X); RNF186(p.Ala64Thr)	[39, 40], [41]
GUCY2C	chr12:14,612,632-14,696,599	Guanylate cyclase 2C	VEO-IBD		Paneth cells (enriched), proximal enterocytes (enriched), intestinal goblet cells (enriched), distal enterocytes (enriched)	Regulates water absorption[42]. Regulates cell proliferation, stem cell differentiation, DNA repair, and endoplasmic reticulum stress[42]. Regulates apoptosis[43].	GUCY2C(G549S), GUCY2C (F525L)	[44], [3]

*hg38, **both aminoacid and gene variant coding is used
abbreviations: LPS, lipopolysaccharide

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