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Microscopy image showing that commensal fungi (green) cohabit with commensal bacteria (red) in the mouse gut. (Courtesy of Iliyan D. Iliev and David M. Underhill, this issue).

Faecalibacterium prausnitzii and human intestinal health

S Miquel^{1,2}, R Martín^{1,2}, O Rossi³, LG Bermúdez-Humarán^{1,2}, JM Chatel^{1,2}, H Sokol^{1,2,4,5}, M Thomas^{1,2}, JM Wells^{3,6} and P Langella^{1,2,6}

Faecalibacterium prausnitzii is the most abundant bacterium in the human intestinal microbiota of healthy adults, representing more than 5% of the total bacterial population. Over the past five years, an increasing number of studies have clearly described the importance of this highly metabolically active commensal bacterium as a component of the healthy human microbiota. Changes in the abundance of *F. prausnitzii* have been linked to dysbiosis in several human disorders. Administration of *F. prausnitzii* strain A2-165 and its culture supernatant have been shown to protect against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice. Here, we discuss the role of *F. prausnitzii* in balancing immunity in the intestine and the mechanisms involved.

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This review comes from a themed issue on Ecology and industrial microbiology

Edited by Jerry M. Wells and Philippe Langella

For a complete overview see the Issue and the Editorial

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Faecalibacterium prausnitzii, a dominant member of the healthy human colon microbiota

Faecalibacterium prausnitzii was initially classified as *Fusobacterium prausnitzii*, but in 1996, the complete sequence of the 16S rRNA gene of different human strains (ATCC 27766 and ATCC 27768) established that they were only distantly related to *Fusobacterium* and were more closely related to members of *Clostridium* cluster IV (the *Clostridium leptum* group) [1,2]. The new nomenclature was definitively adopted in 2002, when Duncan *et al.* [3] proposed that a new genus *Faecalibacterium* be created to include the non-spore-forming and non-motile Gram

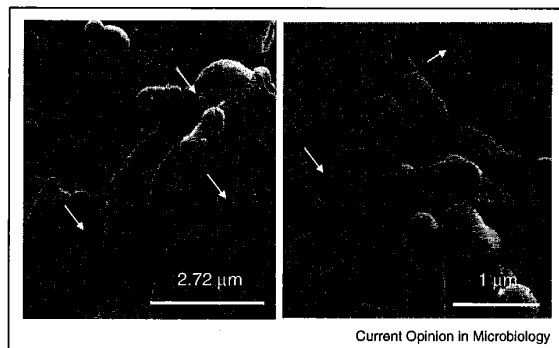
positive bacterium named *Faecalibacterium prausnitzii* (formerly *Fusobacterium prausnitzii*). Today, *F. prausnitzii* species are a major representative of Firmicutes phylum, *Clostridium* class, Ruminococcaceae family.

The first complete genome of the *F. prausnitzii* reference strain A2-165 (DSM17677) was sequenced in 2010 in the frame of the ‘Human Microbiome Project’. Four other complete *F. prausnitzii* genomes have been then sequenced (SL3/3, L2/6, M21/2 and KLE1255) but the annotations are still incomplete. Sequenced *F. prausnitzii* strains appear to lack plasmids and have circular 2.93 to 3.32 Mb chromosomes with an average GC content between 47 and 57% and are predicted to encode around 3000 predicted proteins. In humans, the *Faecalibacterium* genus is divided into two different phylogroups [4*] although it is not known if they have different physiological functions. Scanning electron microscopy (SEM) revealed that the reference strain A2-165 (DSM17677) is a long bacillus of around 2 µm with rounded ends (Figure 1). We observed cell wall extensions, like ‘swellings’ that have not been previously described in this species. Interestingly, the same morphotype was also observed in other *F. prausnitzii* strains from the same phylogroup (data not shown).

F. prausnitzii is an extremely oxygen sensitive (EOS) bacterium and is difficult to cultivate even in anaerobic conditions [3]. The major end products of glucose fermentation by *F. prausnitzii* strains are formate, small amounts of D-lactate (L-lactate being undetectable) and substantial quantities of butyrate (>10 mM butyrate *in vitro*) [3,5]. Recently, culture medium supplemented with flavins and cysteine or glutathione was shown to support growth of *F. prausnitzii* under micro-aerobic conditions [6**]. In the future, it may be possible to generate metabolic maps from genome annotations and transcriptomics data under different fermentative conditions and thereby identify other components that can be added to the medium to enhance growth *in vitro*. Such approaches might permit to increase the viability of *F. prausnitzii* under micro-aerobic conditions and open up possibilities to develop novel probiotic formulations.

F. prausnitzii is a dominant member of the subgroup *C. leptum*, the second most represented in fecal samples (after the *C. coccoides* group) corresponding to ~21% of all prokaryotic cells [7]. It is now generally accepted that *F. prausnitzii* accounts for approximately 5% of the total fecal microbiota in healthy adults but this can increase to around 15% in some individuals [8]. *F. prausnitzii* is

Figure 1



Scanning electron microscopy images of *F. prausnitzii* grown in LYBHI medium. Scale bars are indicated. Arrows indicate cell wall extensions, like 'swellings'.

widely distributed in the Gastrointestinal Tract (GIT) of other mammals such as pigs [9], mice [10] and calves [11] as well as poultry [12,13], and the insect cockroach [14]. The abundance and ubiquity of *F. prausnitzii* suggest that it is a functionally important member of the microbiota with a possible impact on host physiology and health. Changes in the abundance of fecal *C. leptum* group, and in particular *F. prausnitzii*, have been extensively described in different human intestinal and metabolic diseases.

***F. prausnitzii*: an highly metabolic bacteria of the microbiota**

Li *et al.* [15^{*}] demonstrated that *F. prausnitzii* population variation is associated with modulation of eight urinary metabolites of diverse structure, indicating that this species is one of the highly functionally active members of the microbiome [15^{*}]. However, it seems important to better investigate the role of *F. prausnitzii* metabolism on intestinal homeostasis also considering the crosstalk with the other members of microbiota. The recently described gnotobiotic models for *F. prausnitzii* will be useful in discovering effects on the host and its interactions with other species [16^{*}]. Moreover, *F. prausnitzii* is one of the most abundant butyrate-producing bacterium in the GIT [17]. Butyrate plays a major role in gut physiology and it has pleiotropic effects in intestinal cell life cycle and numerous beneficial effects for health through protection against pathogen invasion, modulation of immune system and reduction of cancer progression [18]. In addition, butyrate is proposed to have anti-inflammatory activities in the colon mucosa [19]. For instance, intra-rectal delivery of butyrate producing bacteria has been previously shown to prevent colitis [20]. Thus, by producing butyrate in the gut, *F. prausnitzii* may impact on physiological functions and homeostasis to maintain health. However, specific physiological and health effects of butyrate production by *F. prausnitzii* have not yet been demonstrated [21^{**}].

***F. prausnitzii*: a sensor of health?**

Most data linking abundance of *F. prausnitzii* to health status come from 16S rRNA based profiling of microbiota in inflammatory bowel disease (IBD) of which there is three types Crohn's disease (CD), ulcerative colitis (UC) and Pouchitis. Table 1 summarizes the variation of relative abundance of *F. prausnitzii* in fecal or mucosal samples from IBD patients compared to healthy subjects, using different methods. The data reveal that the relative abundance of *F. prausnitzii* can serve as an indicator or biomarker of intestinal health in adults and low levels could be predictive for CD. CD are notably classified according disease location (ileal CD: ICD, colonic CD: CCD) and it has been shown that CD-associated dysbiosis is not the same in patients with or without ileal involvement. Indeed, *F. prausnitzii* deficiency was first shown in ICD patients [21^{**}]. It has been thus demonstrated that low *F. prausnitzii* level in ICD undergoing surgery is associated with a higher risk of post-operative recurrence [21^{**}]. In 2008, Swidsinski *et al.* [23^{**}] proposed a diagnostic test based on *F. prausnitzii* prevalence and leukocyte count features to distinguish active CD from UC with good sensitivity (79–80% sensitivity and 98–100% specificity respectively). In fact, *F. prausnitzii* depletion ($<1.10^9$ mL⁻¹) along with normal leukocyte counts (>30 leukocytes/10⁴ μm²) is typical in CD, but not UC patients, where a massive increase of leukocyte counts together with high *F. prausnitzii* numbers is observed [23^{**}]. Moreover, even if the host genotype partially determines the microbial community composition in the human gut, concordance of the disease in monozygotic twins is less than 50% indicating that environmental factors play a key role [24]. In fact, bacterial infection-driven dysbiosis and environmental factors are correlated to IBD characterized by an imbalance of mucosal protective bacteria shared by bacteria from the *C. leptum* group including *F. prausnitzii* [22]. However, microbiota profiling in cohorts of patients means we cannot determine which came first the disease or a change in the microbiome. Long-term longitudinal studies in prospective cohorts will be required to establish a causal link between changes in the microbiota and disease progression.

The effects of IBD treatments on *F. prausnitzii* population levels are still unclear, but some show a positive impact on *F. prausnitzii* population in the microbiota. For instance, Rifaximin (reported to induce clinical remission in patients with active CD) is associated with an increased level of *Bifidobacteria* and *F. prausnitzii* [25]. Other specific treatments such as chemotherapy and interferon α-2b were shown to reverse the depletion of *F. prausnitzii* [26]. Moreover, a high-dose cortisol therapy or Infliximab can completely restore *F. prausnitzii* concentrations from zero to higher levels than 1.4×10^{10} bacteria/mL within few days [23^{**}]. This observation suggests that the depletion of *F. prausnitzii* in active CD is not a causative

Table 1

***F. prausnitzii* variations in the microbiota of different IBD cohorts compared to healthy subjects**

Diseases	Samples	Techniques	n	Mean ages	<i>F. prausnitzii</i> variations	Ref
UC	Colonic	Sequencing 16S rRNA	1	12	↑	[50]
UC	Fecal	FISH	105	41.2 (18–84)	↑	[23**]
UC	Fecal	PCR	14	ND	→	[51]
UC	Colonic biopsy	Pyrosequencing/RT-PCR	12	13.0 (8.5–15.8)	→	[52]
R-UC	Fecal	RT-qPCR	4	35 (±4.3)	→	[22]
UC	Mucosal pouch biopsy	Sequencing 16S rRNA	8	51 (19–63)	↓	[53]
UC	Fecal	<i>In vitro</i> : M-SHIME	6	40.5 (33–78)	↓	[54]
UC	Fecal	Real time PCR	22	38.4 (±11.3)	↓	[55]
A-UC	Fecal	RT-qPCR	13	39.7 (±3.5)	↓	[22]
Pouchitis	Mucosal biopsy	Sequencing 16S rRNA	8	39 (19–64)	→	[53]
Pouchitis FAP	Mucosal biopsy	Sequencing 16S rRNA	3	32 (30–54)	→	[53]
CD	Colonic biopsy	Pyrosequencing/RT-PCR	13	12.2 (8.0–16.3)	↑	[52]
CD	Biopsy	PCR-DGGE	19	36.7 (±3.72)	↓	[56]
CD	Fecal	FISH	82	34.8 (17–78)	↓	[23**]
CD	Fecal	PCR	20	ND	↓	[51]
CD	Fecal	RT-qPCR/microarray	16	31(25–39)	↓	[57]
CD	Fecal	FISH	50	39 (19–68)	↓	[26]
CD	Fecal	FISH	28	44.3 (21–76)	↓	[46]
CD	Fecal	DGGE	68	45 (25–76)	↓	[58]
CD	Fecal	RT-qPCR	47	35.3 (±9.4)	↓	[59]
CD	Fecal	Real time PCR	20	31.2 (±14.1)	↓	[55]
RCD	Fecal	RT-qPCR	10	39.1 (±4.2)	→	[22]
RCD	Fecal	GoArray	6	31 (18–44)	↓	[60]
ACD	Fecal	RT-qPCR	22	36.9 (±3.3)	↓	[22]
ACD	Mucosa associated	FISH	ND	ND	↓	[21**]
ACD	Fecal	FISH	103	ND	↓	[61]
ICD	Mucosa associated	RT-qPCR	6	50.8 (±4.5)	↓	[24]
ICD	Ileal biopsy	qPCR	18	35.2 (18–58)	↓	[62]
CCD	Mucosa associated	RT-qPCR	8	49 (±18.5)	→	[24]

UC, ulcerative colitis; AUC, active-ulcerative colitis; RUC, remission-ulcerative colitis; FAP, familial adenomatous polyposis; CD, Crohn's disease; ACD, active Crohn's disease; RCD, remission Crohn's disease; CCD, colonic Crohn's disease; ICD, ileal Crohn's disease; ND, not determined.

event but rather a consequence of intestinal inflammation which can specifically eradicate for example EOS bacteria through the excess of reactive oxygen species [23**]. However, as *F. prausnitzii* has been shown to exhibit both *in vitro* and *in vivo* anti-inflammatory effects [21**], a negative effect of a decrease of *F. prausnitzii* levels cannot be completely ruled out and suggests that this bacterium might also contribute to homeostasis in a healthy gut. In fact, we recently showed in the first gnotobiotic model with *F. prausnitzii* that it could influence gut physiology through mucus pathway and the production of mucus O-glycans [16*].

Irritable bowel syndrome (IBS)

The intestinal microbiota of IBS patients differed significantly from that of healthy subjects with a twofold increased in the Firmicutes to Bacteroidetes ratio [27]. A negative correlation has been observed between the abundance of *Faecalibacterium*-related bacteria and IBS symptoms. IBS-A (alternating-type IBS) patients have significantly lower levels of *Faecalibacterium* spp. This is a common signature found in IBS-associated and IBD-associated microbiota which provides a molecular basis for the observation that some features of IBS, such as micro-inflammation, are shared with IBD, particularly during remission periods [27]. In contrast to IBS-A,

F. prausnitzii is not modified in IBS-D (diarrhea-predominant) and is notably lower or not modified in IBS-C (constipation-predominant IBS) patients [27–29]. This observation suggests that only the IBS-A form is associated with lower *F. prausnitzii* counts.

Obesity

While a connection between microbiota and obesity-related disorders has been established, the underlying mechanisms and microbiota changes are still poorly understood [30]. The ratio of Firmicutes to Bacteroidetes is altered in overweight and obese subjects but not others. In addition, the presence of *F. prausnitzii* species has been linked to the reduction of low-grade inflammation in obesity and diabetes independently of caloric intake [31,32]. However, *F. prausnitzii* levels were significantly higher in south Indian obese children than in non-obese participants [33]. Owing to the inconsistencies in correlating *F. prausnitzii* with obesity in different cohorts, its role in this metabolic disorder is still uncertain and requires further studies [31,32].

Coeliac disease

This is a chronic inflammatory disorder of the small intestine, characterized by a permanent intolerance to dietary gluten in genetically predisposed individuals. The

relative proportion of *F. prausnitzii* has been shown to be significantly reduced in patients [34] and after a gluten-free diet in healthy adults [35]. Interestingly, a similar trend was detected in duodenal biopsies of untreated or treated coeliac disease children compared with controls [36]. Different hypotheses could explain these changes: firstly, the activation of the adaptive and innate immune response; and/or secondly, the reduction in polysaccharides intake, since these dietary compounds usually reach the distal part of the colon, and constitute one of the main energy sources for beneficial components of gut microbiota.

Other diseases

Fecal abundance of *F. prausnitzii* has also been analyzed in other diseases such as self limited colitis [22], atopic diseases [37], chronic idiopathic diarrhea [38], acute appendicitis [39], neuroendocrine tumors of the midgut [26], liver transplantation [40] and colorectal cancer (CRC) [41].

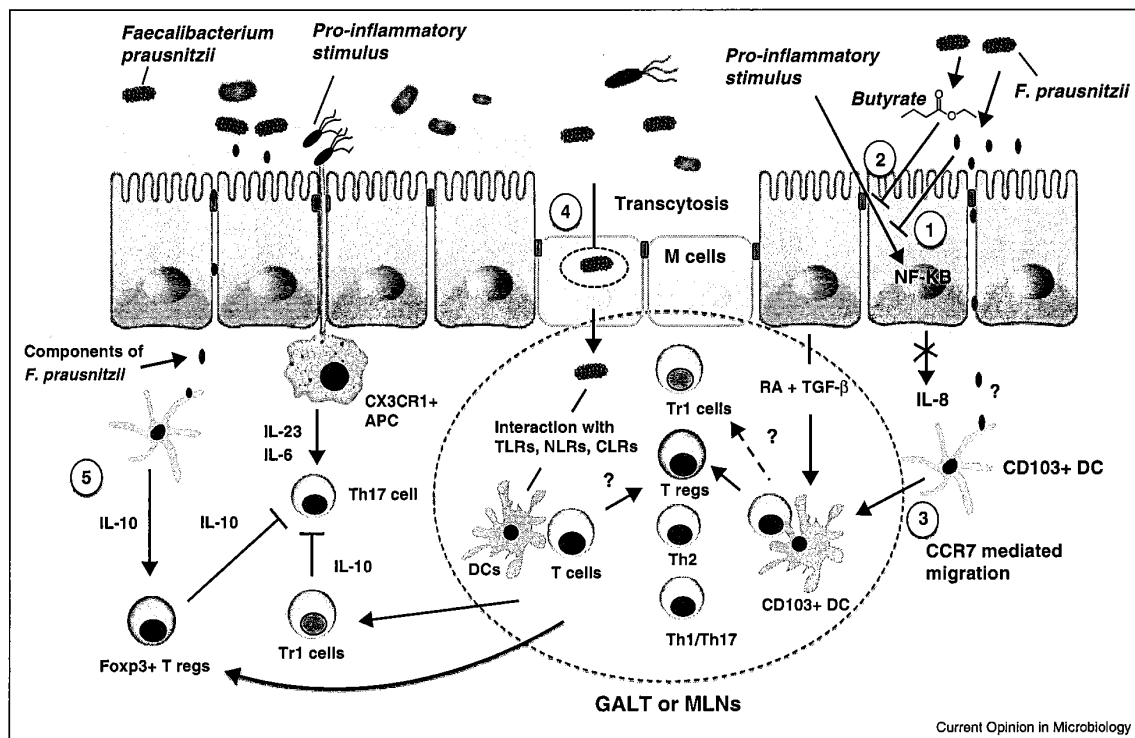
On the basis of the huge quantity of scientific data in diseased and healthy subjects we conclude that *F. prausnitzii*

abundance in the microbiota is a good intestinal health indicator, except in UC patients. This was surprising given the clear relationship between active disease in CD patients and low abundance of *F. prausnitzii*. Moreover, most studies give support to the notion that this bacterium is very sensitive to its environment; its proportion negatively correlates with the presence of acute or moderate inflammation. A systematic evaluation of *F. prausnitzii* in patients feces, based on the analysis of the gut microbiota or components of the microbiota, could be useful to develop therapeutic strategies and personalized medicine. However, the routine diagnostic tools to detect *F. prausnitzii* dysbiosis in clinical laboratories are not yet developed and due to its sensitivity to the oxygen, molecular detection techniques will need to be developed as prognostic markers of disease therapy.

Possible mechanisms of *F. prausnitzii* anti-inflammatory effects

F. prausnitzii and its culture supernatant can attenuate 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice [21**]. This highlights its potential to be exploited as a therapeutic for IBD but until now, the

Figure 2



Proposed anti-inflammatory mechanisms of *F. prausnitzii*. 1. The supernatant of *F. prausnitzii* blocks NF-κB activation induced by a pro-inflammatory stimulus [21**]. 2. Butyrate produced by *F. prausnitzii* inhibits NF-κB activation in mucosal biopsies. 3. *F. prausnitzii* components might interact with CD103+ dendritic cells (DCs) in the lamina propria and stimulate their migration to mesenteric lymph nodes (MLN) and the induction of Tregs. 4. M cell transcytosis of *F. prausnitzii* in organized lymphoid structures may induce Tregs. 5. The capacity of *F. prausnitzii* to induce high amounts of IL-10 in antigen presenting cells may enhance the suppressive activity of Foxp3+ Tregs and block Th17 cells induced by pro-inflammatory stimuli.

active molecule(s) that directly impact the host immune response and the precise mechanisms involved are not known. One possible mechanism is attributed to secreted component(s) of *F. prausnitzii* culture supernatant that inhibited NF- κ B activation and IL-8 secretion induced by IL-1 β in Caco-2 cells (Figure 2) [21**]. The production of butyrate was shown to have only a slight impact in the suppression of inflammation by live *F. prausnitzii* in the mouse TNBS colitis model [21**]. This suggests that another metabolite or factor produced during anaerobic growth would play a major role. We are currently searching for these factors using metabolomic, biochemical and genetic approaches. Further studies are needed to determine whether such anti-inflammatory factor can attenuate the NF- κ B activation in immune cells and primary epithelial cells which would provide further evidence for its role in prevention of colitis. Other possible mechanisms contributing to the protective effect of *F. prausnitzii* in colitis might be related to its capacity to induce relatively large amounts of IL-10 and low amounts of IL-12 in peripheral blood mononuclear cells [21**]. If *F. prausnitzii* also induces large amounts of IL-10 in mucosal dendritic cells and macrophages, it may contribute to intestinal homeostasis by inhibiting the production of pro-inflammatory cytokines such as IFN- γ , TNF- α , IL-6 and IL-12 and enhancing the suppressive activity of Foxp3+ Tregs in the mucosa [42] (Figure 2). The induction of IL-10 in immune cells by *F. prausnitzii* may also play a role in shaping T cells responses, in particular in the induction of Tregs in the colon as described for certain other commensals [43–45]. Moreover, the amount of TLR4 in human intestinal DCs is negatively correlated with *F. prausnitzii* level suggesting that intestinal DC function may be influenced by this bacterium [46].

Conclusion

F. prausnitzii, is a major EOS component of the intestinal microbiota which has been largely ignored until recently. Its low prevalence in many intestinal disorders, particularly in IBD patients, suggests its potential as an indicator of intestinal health. *F. prausnitzii* is a butyrate producer and has demonstrated anti-inflammatory effects *in vitro* and *in vivo* using a mouse colitis model making it a key member of the microbiota that may contribute to intestinal homeostasis. Thus, modulation of *F. prausnitzii* abundance, for example using prebiotics and/or probiotics and/or formulations that permit survival through the upper part of the intestinal tract might have prophylactic or therapeutic applications in human health. For instance, the fiber inulin has well-characterized impact on microbiota composition inducing specific and significant increase in *Bifidobacterium* and *F. prausnitzii* [47,48]. Moreover the rapid detection of *F. prausnitzii* abundance in feces warrants further investigation as a biomarker of intestinal health.

Experimental procedures

Scanning electron microscopy

Scanning electron microscopy analyses were performed on the MIMA2 platform (INRA, Massy, France). 1 mL of pure culture in LYBHI medium was pelleted, resuspended and then fixed in 200 μ L of glutaraldehyde, 3% ruthenium red for two hours in an anaerobic chamber and then stored at 4 °C. Scanning electron microscopy was performed as reported previously [49].

Conflict of interest

The authors have no conflicting financial interests.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

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