FEMS Microbiology Reviews, 2023, 47, 1–18
DOI: 10.1093/femsre/fuad039
Advance access publication date: 14 July 2023
Review Article

Faecalibacterium: a bacterial genus with promising human health applications

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Editor: [Oscar Kuipers]

Abstract

In humans, many diseases are associated with alterations in gut microbiota, namely increases or decreases in the abundance of specific bacterial groups. One example is the genus *Faecalibacterium*. Numerous studies have underscored that low levels of *Faecalibacterium* are correlated with inflammatory conditions, with inflammatory bowel disease (IBD) in the forefront. Its representation is also diminished in the case of several diseases, including colorectal cancer (CRC), dermatitis, and depression. Additionally, the relative presence of this genus is considered to reflect, at least in part, intestinal health status because *Faecalibacterium* is frequently present at reduced levels in individuals with gastrointestinal diseases or disorders. In this review, we first thoroughly describe updates to the taxonomy of *Faecalibacterium*, which has transformed a single-species taxon to a multispecies taxon over the last decade. We then explore the links discovered between *Faecalibacterium* abundance and various diseases since the first IBD-focused studies were published. Next, we examine current available strategies for modulating *Faecalibacterium* levels in the gut. Finally, we summarize the mechanisms underlying the beneficial effects that have been attributed to this genus. Together, epidemiological and experimental data strongly support the use of *Faecalibacterium* as a next-generation probiotic (NGP) or live biotherapeutic product (LBP).

Keywords: *Faecalibacterium*, keystone, next-generation probiotic, live biotherapeutic product, anaerobe, commensal, inflammation

Introduction

Faecalibacterium is a genus of strictly anaerobic, extremely oxygen-sensitive (EOS), Gram-positive, rod-shaped, nonmotile, and nonspore-forming bacteria (Duncan et al. 2002a). Initially, it was thought to account for 5% of the human microbiota (Qin et al. 2010). Based on a metagenomic analysis of over 7900 human samples, a more recent study has suggested the mean and median may be 6.5% and 4.8%, respectively, in adults and could may even be as high as 75% (De Filippis et al. 2020). These results confirm the high relative abundance of this genus in the human gut. Moreover, *Faecalibacterium* is prevalent in human populations across the world—it was detected in 85% of gut samples (De Filippis et al. 2020)—and members of *Faecalibacterium* are considered to be ubiquitous in the gastrointestinal tracts (GITs) of healthy humans (Tap et al. 2009). Research also indicates that *Faecalibacterium* levels differ with age and potentially gender, where abundances are lower in women than in men (Aguirre de Carcer et al. 2011). Additionally, the prevalence of this genus is less pronounced in newborns, children, and the elderly (De Filippis et al. 2020). It is first detected around 6–7 months of age and persists at a low level until 2–3 years of age (Hopkins et al. 2005). This pattern in early infancy suggests that there must be a first wave of gut colonization for *Faecalibacterium* to become established. Indeed, the implantation of EOS bacteria depends on certain physicochemical conditions that are generated by other commensal bacteria (Tomas et al. 2013). *Faecalibacterium* abundance is higher in non-Westernized populations, highlighting its ancient synergistic relationship with humans that has only recently been disrupted by modern lifestyles (De Filippis et al. 2020). It has also been hypothesized that *Faecalibacterium* might act to stabilize the gut microbiota. Support for this idea was found in a study that monitored the microbiota of healthy human subjects over the course of a year: the abundance of this genus was negatively correlated with greater intraindividual variability in microbiota composition (Olsson et al. 2022), suggesting its potential role as a keystone taxon (Tudela et al. 2021). In this vein, *Faecalibacterium* is among the first genus of commensal bacteria to have been found to differ between individuals with and without inflammatory bowel disease (IBD), and its beneficial role appears to be associated with its anti-inflammatory properties (Sokol et al. 2008).

The genus *Faecalibacterium*

From a single species to multiple species

Faecalibacterium has undergone several taxonomic shifts since its discovery in 1922 by J. Prausnitz (Prausnitz 1922). Initially classified as *Bacteroides prausnitzii* in 1937 by Hauduroy et al. (1937), it was reclassified as *Fusobacterium prausnitzii* in 1974 (Cato et al.1974) and then as *Faecalibacterium prausnitzii* in 2002 (Duncan et al. 2002a) (Fig. 1). Initially, *F. prausnitzii* was the only member of the genus and was represented by two cultured strains—ATCC 27768 (the type strain) and ATCC 27766—as well as by

Received 5 January 2023; **revised** 8 June 2023; **accepted** 12 July 2023

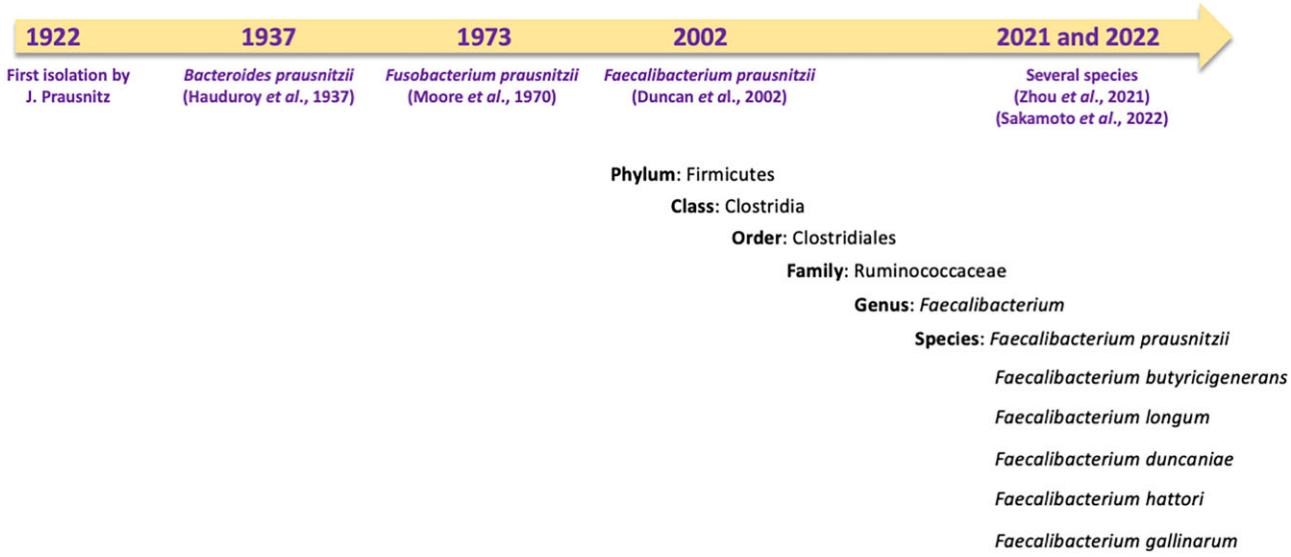

Figure 1. *Faecalibacterium* taxonomy and evolutionary timeline.

two newly discovered strains (A2-165 and L2-6) (Duncan et al. 2002a). Despite its high prevalence and abundance, it has been challenging to isolate and culture this genus because its EOS status. In recent years, it has been possible to isolate *Faecalibacterium* strains using classical strategies, such as microbiological flow charts (Martin et al. 2017), or more complex strategies, including flow cytometry-assisted sorting under anaerobic conditions using anti-*Faecalibacterium* polyclonal antibodies (Bellais et al. 2022). Thanks to advances in anaerobic cultivation and next-generation sequencing techniques, the complexity of the genus has progressively been deciphered. First, a 16S rRNA gene-based approach divided *F. prausnitzii* into two phylotypes, which accounted for 97.9% of the amplified sequences found across several studies (Lopez-Siles et al. 2012). In 2017, an analysis of 17 *Faecalibacterium* isolates led to the identification of three phylotypes (A, B, and C) (Benevides et al. 2017). However, several strains did not belong to any of these phylotypes, setting the basis for the future identification of additional species. The number of phylogroups increased as a result of research comparing the average nucleotide identity (ANI) of 35 genomes (Fitzgerald et al. 2018). In 2020, more than 7900 human and 200 nonhuman primate metagenomes were analyzed leading to the identification of 22 *Faecalibacterium*-like metagenome-assembled genomes (MAGs) (De Filippis et al. 2020). A total of 12 were specific to humans, distributed across the globe, and displayed a degree of age-related variation. The others were specific to other particular niches (De Filippis et al. 2020). In 2021, following genome sequencing and phenotypic, chemotaxonomic, and phylogenetic characterization, two new species of *Faecalibacterium* were described: *Faecalibacterium butyricigenerans* (type strain: AF52-21^T) and *Faecalibacterium longum* (type strain: CM04-06^T) (Zou et al. 2021). Finally, in 2022, three novel species were proposed: *Faecalibacterium duncaniae* (type strain: A2-165 of human origin), *Faecalibacterium hattorii* (type strain: APC922/41–1^T of human origin), and *Faecalibacterium gallinarum* (type strain: ic1379^T of chicken/broiler origin) (Sakamoto et al. 2022). The type strain for *F. prausnitziii* remains ATCC 27768. The complexity of this genus is still being uncovered: recent phylogenetical analysis revealed that several strains do not seem to belong to any of the above species (Fig. 2) (Tanno et al. 2022). The discovery of new phylogroups and species has expanded possibilities for studying and understanding the general characteristics of this genus and the role it plays in host health. In a recent study, Tanno et al. (2023) found that 16S rRNA is not a suitable gene marker for quantifying *Faecalibacterium* due to sequence divergence within clusters/strains and even among copies of a single strain, which could lead to biased results (Tanno et al. 2022). The same group recently proposed that *rpoA* may serve as a better gene marker for identifying *Faecalibacterium* spp. (Tanno et al. 2023). These important results indicate that the knowledge gathered prior to the discovery of these new phylogroups and species is inaccurate because adequate tools were lacking. They also signal that new analyses must be performed that account for genus diversity and that utilize appropriate gene markers, notably in the case of studies that used the 16S gene (Tanno et al. 2022).

General metabolism and metabolic cross-feeding

Acetate, propionate, and butyrate are among the most abundant short-chain fatty acids (SCFAs) in the human gut (Martin-Gallausiaux et al. 2021). They are the primary end products resulting from bacterial fermentation of dietary fibers, including plant cell wall polysaccharides, resistant starches, soluble oligosaccharides, and endogenous products (e.g. mucin). Additionally, some bacterial species can ferment amino acids and proteins to produce SCFAs and branched fatty acids. Butyrate is the main energy source of colonocytes and plays a central role in host physiology (Martin-Gallausiaux et al. 2021). The major end products of glucose fermentation by *Faecalibacterium* strains are formate, small amounts of D-lactate (L-lactate is undetectable), and large amounts of butyrate (>10 mM *in vitro*) (Duncan et al. 2002a, Miquel et al. 2013).

Cross-feeding occurs when a species metabolizes metabolites produced by another species (D'Souza et al. 2018). SCFAs in particular acetate, are among the most common cross-fed metabolites in the bacterial communities of the human gut (D'Souza et al. 2018). Acetate consumption is the major driver of butyrate production by members of *Faecalibacterium* genus (process known as acetate-cross feeding) in the healthy human gut (Miquel et al. 2013). The key enzyme in butyrate production is butyryl-CoA:acetate CoA-transferase (Fig. 3). It catalyzes the reaction whereby butyrate and acetyl-CoA are generated from extracellular acetate and intracellular butyryl-CoA, thus

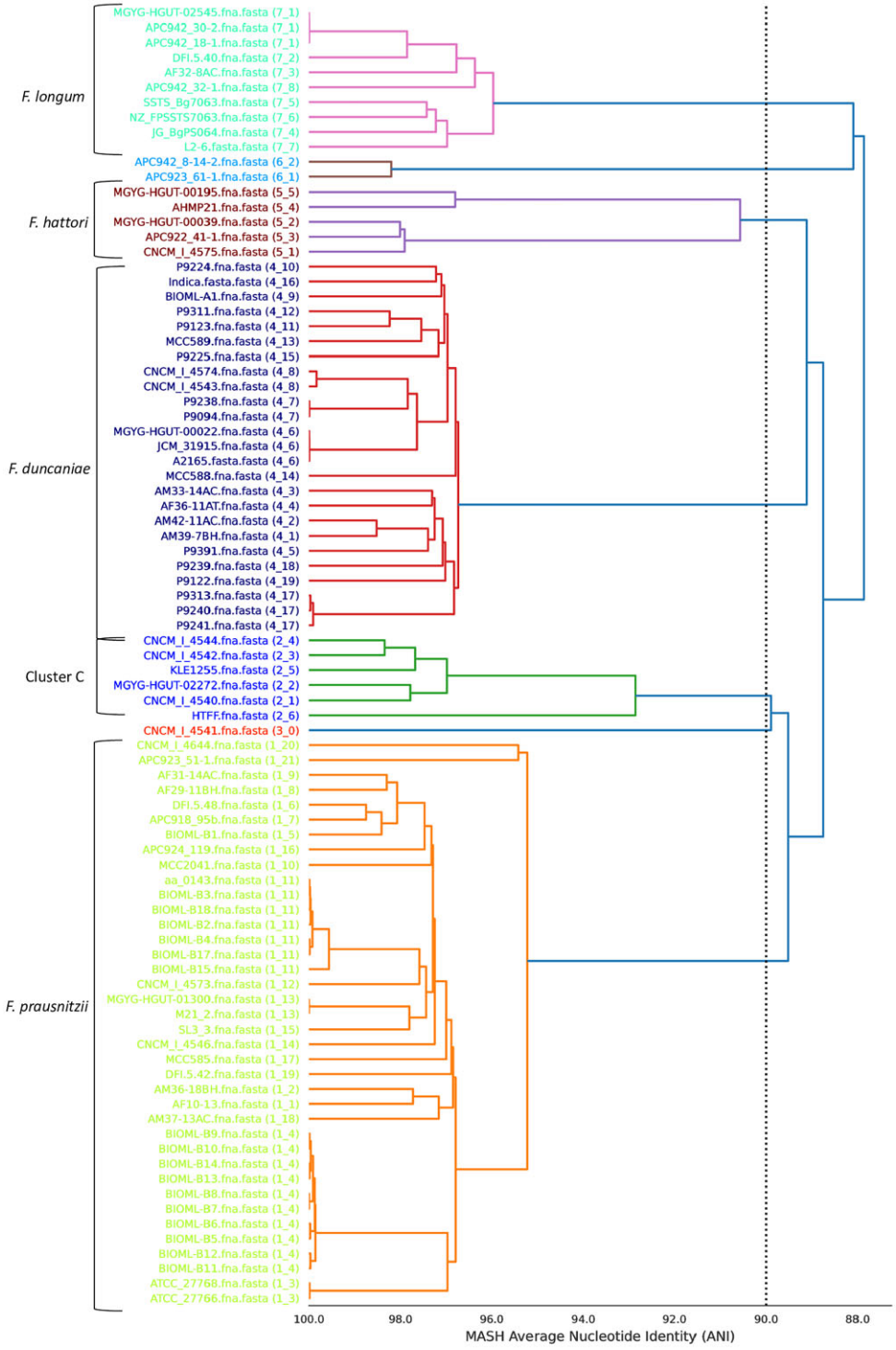

Figure 2. ANI-value-based hierarchical clustering of *Faecalibacterium* genomes. Complete or draft genome sequences of *Faecalibacterium* strains were obtained from the NCBI database. The program dRep (version 3.2.2) was run using the 87 available *Faecalibacterium* genomes as input (Olm et al. 2017). ANI values of 95% or higher indicate that a genome pair likely belongs to the same species, whereas ANI values below 95% indicate that a genome pair likely represents different species. Cluster C corresponds to phylogroup C, as described elsewhere (Benevides et al. 2017).

explaining the growth-promoting effects of acetate consumption (Duncan et al. 2002a,b, 2004, Charrier et al. 2006, Heinken et al. 2014). Indeed, supplementing the culture medium with acetate (33–50 mM) stimulates *Faecalibacterium* growth (Duncan et al. 2002a, Lopez-Siles et al. 2012, D'Hoe et al. 2018). In a co-culture model, butyrate production by *Faecalibacterium* was increased via acetate cross-feeding with the acetate-producing bacteria *Bifidobacteria adolescentis* (Rios-Covian et al. 2015) and *Blautia hydrogenotrophica* (D'Hoe et al. 2018) (Fig. 3). In research using gnotobiotic rodents colonized by *F. duncaniae* and *Bacteroidetes thetaiotaomicron*, the phenomenon was observed *in vivo* by measuring butyrate and acetate levels in cecal samples (Wrzosek et al. 2013).

Metabolic cross-feeding has been performed between *F. duncaniae* A2-165 and lactic acid bacteria (LAB) using *F. duncaniae*

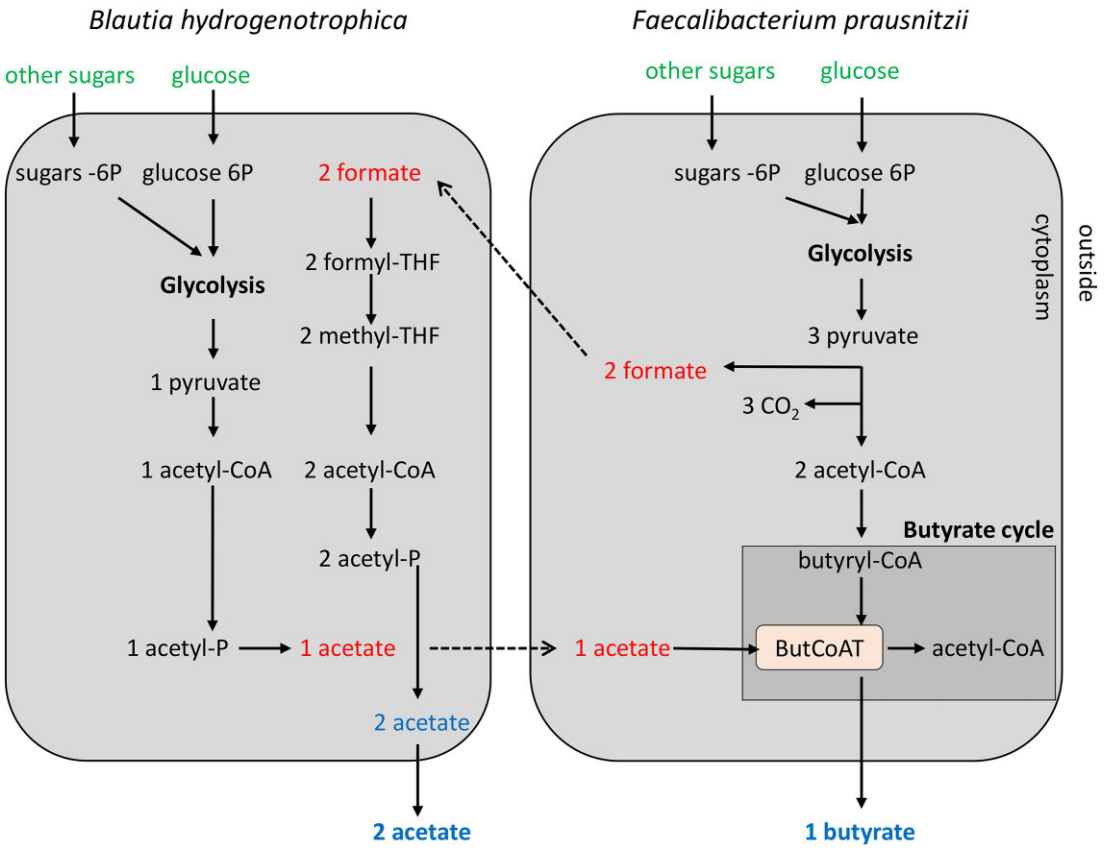

Figure 3. Acetate and formate cross-feeding between *B. hydrogenotrophica* and *F. prausnitzii*. The metabolism of *B. hydrogenotrophica* centers on glycolysis and the acetate pathway. The metabolism of *F. prausnitzii* centers on glycolysis and the formate and butyrate pathways**.** The key enzyme in butyrate production is butyryl-CoA:acetate CoA-transferase (ButCoAT). In red are the SCFAs consumed (acetate, formate). In blue are the SCFAs produced (acetate, butyrate). In green are the sugars consumed.

A2-165 cultured with cell-free supernatants (8% v/v) obtained from LAB grown in an acetate-rich, vitamin-poor medium (Lebas et al. 2020). A transcriptomics approach was used to characterize four LAB strains stimulating *F. duncaniae* A2-165 growth or delaying its lysis. These strains were *Lactococcus lactis subsp. lactis* CNCM I-1631, *subsp. cremoris* CNCMI-3558, *Lactobacillus paracasei* CNCM I-3689, and *Streptococcus thermophilus* CNCM I-3862. The results revealed that the supernatants had some shared effects, namely the upregulation of carbohydrate metabolism genes and cell wall-related genes as well as the downregulation of replication and mobilome genes. There were also LAB-specific effects. In particular, *F. prausnitzii* answer to the exposure of *L. paracasei* CNCM I-3689 supernatant, may stabilize cell wall formation, through the upregulation of some genes involved mainly in peptidoglycan formation, and the inhibition of cell wall degradation genes. This *in vitro* study suggests that LAB metabolites other than acetate may modify the metabolism of *F. duncaniae* A2-165.

While other members of the gut microbiome, such as *B. thetaiotaomicron* or *Bifidobacterium*, are known to be effective degraders and utilizers of polysaccharides, members of *Faecalibacterium* are less well-equipped to utilize complex carbon sources (Heinken et al. 2014). Indeed, the genome of *F. duncaniae* A2-165 (3.11 Mb) contains genes for just 31 glycoside hydrolases and one polysaccharide lyase. In contrast, the genome of *B. thetaiotaomicron* VPI 5482 contains genes for 255 glycoside hydrolases and 29 polysaccharide lyases (6.36 Mb). Moreover, glycolytic ability is likely strain dependent, as suggested by an *in silico* study (Blanco et al. 2019).

The second most relevant and best-documented compound involved in *Faecalibacterium* crossfeeding is fructose, which can result from the degradation of inulin, a dietary fiber and complex sugar (Ramirez-Farias et al. 2009). Even with limited carbohydrate-degradation machinery (Heinken et al. 2014), some *Faecalibacterium* members can metabolize inulin and pectin (Lopez-Siles et al. 2012, Rios-Covian et al. 2015, Martin et al. 2017). Research on inulin metabolism in *Faecalibacterium* was first explored in an interventional study where healthy volunteers took inulin supplements for 16 days. The result was an increase in populations of *Faecalibacterium* and *B. adolescentis*, with a concomitant increase in butyrate production (Ramirez-Farias et al. 2009). Under laboratory conditions, 9 of 11 strains were able to ferment inulin, but only two displayed efficient growth (Lopez-Siles et al. 2017). When *Faecalibacterium* metabolizes inulin, different products are released that can serve as substrates for other community members, thus contributing to broader-scale cross-feeding (Rios-Covian et al. 2015, Moens et al. 2016). Inulin degradation (glucosyl hydrolases) and uptake (ABC transporter) mechanisms were recently described in *F. duncaniae* A2-165 (Park et al. 2022). For this same strain, research has provided a molecular characterization of the phosphoenolpyruvate:carbohydrate phosphotransferase system transporter (PTS) involved in fructose uptake (EI,HPr and EIIABC^{Fru}, the general and specific PTS components, respectively) using the membranous protein extracts from cells grown on diverse carbohydrates and the purified PTS proteins (Kang et al. 2021). This result is consistent with the proteomic

analysis of Park et al. (2022). Indeed, the fructose-specific PTS proteins were highly upregulated during growth in inulin (Park et al. 2022). Overall, the results suggest that teasing apart PTS functionality in *Faecalibacterium* could clarify how this taxon outcompetes other bacterial taxa in the human intestine.

Faecalibacterium can also take advantage of compounds generated by other members of the microbiome community, such as the products resulting from the degradation of ß-mannan complex polysaccharides, which are important components of hemicelluloses in plant cell walls. These products are released by metabolic processes in *Bacteroides ovatus* or *Roseburia intestinalis*, via a pathway encoded by specific, highly conserved genes with a worldwide distribution (Lindstad et al. 2021). *Faecalibacterium* is also able to metabolize the products of alginate metabolism released by *Bacteroides* species (Murakami et al. 2021).

Members of *Faecalibacterium* can also use other metabolites, such as *N*-acetylglucosamine, D-glucosamine, and D-glucuronic acid, allowing them to grow on substrates derived from their host, their host's diet, and other bacteria (Lopez-Siles et al. 2012). Some *Faecalibacterium* can breakdown other, more unique compounds, such as avenanthramides—the phenolic alkaloids found in oats. Indeed, *Faecalibacterium* is the only known genus capable of transforming avenanthramides into dihydro-avenanthramides, bioactive compounds with anti-inflammatory and antioxidant properties in specific-pathogen free (SPF) and monocolonized mice (Wang et al. 2021).

Oxidative stress

Although members of *Faecalibacterium* are considered to be EOS, *F. duncaniae* A2-165 can grow under low-oxygen conditions because it possesses an extracellular electron shuttle of flavins and thiols that transfers electrons to oxygen (O_2) (Khan et al. 2012). This mechanism probably involves a flavin reductase, which might regenerate NAD^+ from NADH and reduce O_2 to H_2O_2 (Heinken et al. 2014). In addition, the health benefits of *Faecalibacterium* are directly related to the colon's environmental conditions, given that O_2 dynamics play a central role in intestinal homeostasis (Fig. 4). In the GIT of healthy individuals, O_2 concentrations decrease longitudinally, from the stomach (∼5%) to the colon (0.1%–0.4%), and transversely, from the epithelial cells (5%) to the lumen (1%–2%) (Keeley and Mann 2019). Little is currently known about the relationship between variation in luminal O_2 concentrations and intestinal diseases, including the subsequent effects on hosts. However, many gastrointestinal diseases are thought to be associated with high oxidative stress, which can influence luminal O_2 levels and lead to dysbiosis (Singhal and Shah 2020). As chronic gut inflammation progresses, it can result in uncontrolled and persistent oxidative stress, where reactive oxygen species (ROS), such as H_2O_2, are overproduced and/or inadequately removed by antioxidant systems (Aviello and Knaus 2017, Burgueno et al. 2019). Thus, during gut inflammation, O_2 and ROS levels may present a challenge for *Faecalibacterium* species. Indeed, one of the characteristics associated with IBD is a pronounced decrease in *Faecalibacterium* abundance in the gut (Sokol et al. 2009, Cao et al. 2014). Interestingly, compared to healthy individuals, certain patients with gut inflammation display relatively higher levels of *F. longum* L2-6 and relatively lower levels of *F. duncaniae* A2-165, suggesting that different *Faecalibacterium* species cope differently with oxidative stress (Song et al. 2016, Zhang et al. 2018).

Little is known about how members of *Faecalibacterium* may remain unaffected by O_2 and ROS except that, *in vitro*, *F. duncaniae* A2-165 has been found to have extracellular antioxidants, which transfer electrons to O_2 in moderately oxygenated environments (Khan et al. 2014). Furthermore, when inorganic nitrate was used as an antioxidant, the *Faecalibacterium* population was maintained following total body irradiation in a mouse model (Wang et al. 2020). In addition, using a metabolic model exploring the effects of diet on O_2 sensitivity, it was predicted that diets with a balanced carbohydrate and protein ratio could increase the O_2 range over which *Faecalibacterium* could survive (Henson and Phalak 2017). Thus, the presence of antioxidants as well as relative dietary quantities of carbohydrates and proteins could impact the ability of *Faecalibacterium* species to tolerate oxidative stress during gut inflammation.

Faecalibacterium in relation to health and disease

When the normal microbial ecosystem is altered, various non-predominant bacteria (mainly pathobionts) may thrive, a situation, i.e. sometimes associated with illness (Caballero-Flores et al. 2022). Such dynamics have been linked to many different types of diseases that may or may not be directly related to the GIT. Notably, the abundance of some *Faecalibacterium* species has been found to be altered across a wide range of diseases and disorders. It is essential to note that most of the results presented in this section are based on observational data, which do not allow to determine whether dysbiosis is the cause or consequence of disease. Therefore, these findings should be interpreted with caution. Indeed, the new taxonomic structure of the genus highlights the need for further research, particularly in the case of poorly studied diseases. Lastly, most of the intervention-focused or mechanistic studies described below have been performed in mice, which means that the relevance of their results in humans remains to be assessed.

Inflammatory bowel diseases (IBDs)

The two forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Both are chronic conditions characterized by the heightened chronic activation of the gut mucosal immune system (Khor et al. 2011). This overactive immune response occurs in tandem with an imbalance in the gut microbiota: a decline in *Faecalibacterium* abundance has been observed in CD and UC (Sokol et al. 2008, Morgan et al. 2012). In addition, in IBD, there is a reduction in the richness of two mucosa-associated *Faecalibacterium* phylotypes (Lopez-Siles et al. 2015). The markers for IBD and its subtypes (with or without effects on the ileum) have revealed interesting patterns in a metaproteomics study that compared healthy individuals to individuals with the disease: the latter had reduced levels of *Faecalibacterium* (Henry et al. 2022). In CD patients with ileal involvement, the abundance of *Faecalibacterium* phylogroup II was lower (Lopez-Siles et al. 2016). In another study with the same target population, this decrease was associated with an increase in the levels of primary and secondary bile acids (Gonzalez et al. 2022). Such reductions in *Faecalibacterium* abundance have been linked to the decreased circulation of $CCR6^+CSCR6^+DP8\alpha$ regulatory T (Treg) leukocytes and increased values of disease activity metrics (Sarrabayrouse et al. 2014, Touch et al. 2022). Based on the above evidence, *Faecalibacterium* has been identified as playing a key role in inducing this subset of Treg cells, which have an important influence on microbiota–host cross-talk in cases of IBD. In individuals with active IBD, $DP8\alpha$ leucocytes from the peripheral blood and lamina propria do not respond to *Faecalibacterium*, whereas those from

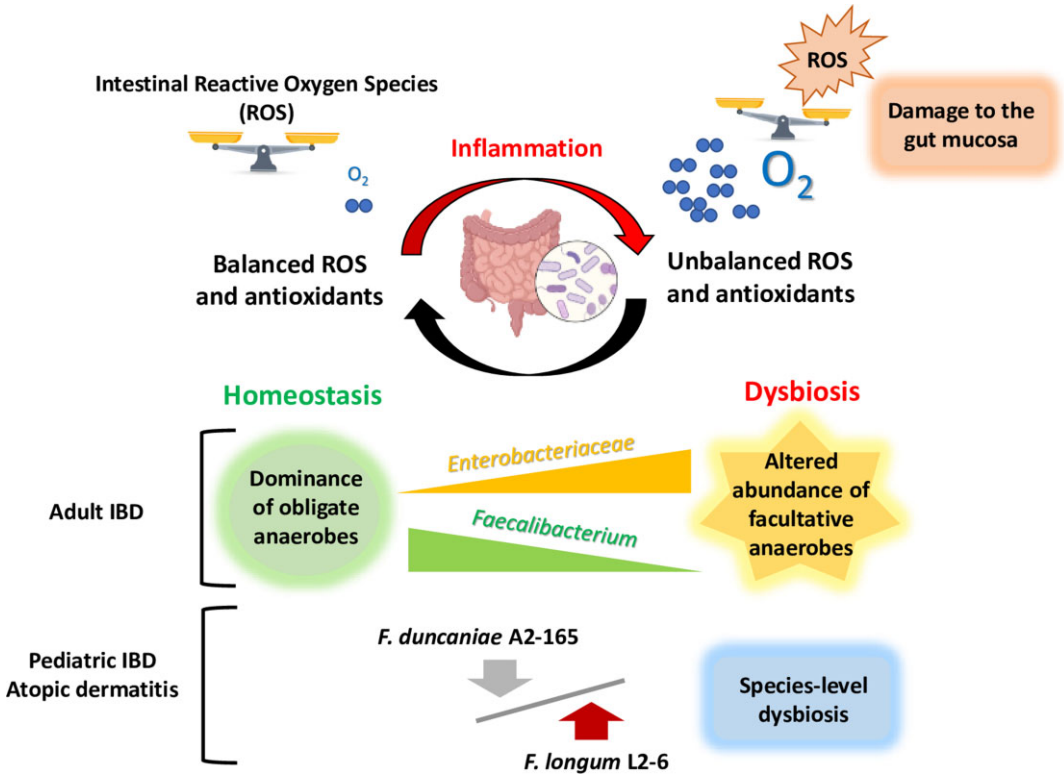

Figure 4. Graphic summary of relationships between *Faecalibacterium* representation within the intestinal microbiota and colon inflammation. The normal state of the microbiota greatly contrasts with the dysbiosis often encountered in digestive diseases such as IBD. Intestinal inflammation is accompanied by an overproduction of ROS as well as an increase in O_2 levels, conditions that favour facultative anaerobes over strict aerobes such as *Faecalibacterium*. In some patient cohorts, abundance of *F. duncaniae* A2-165 decreases while that of *F. longum* L2-6 increases (Song et al. 2016, Zhang et al. 2018).

individuals who are healthy or in remission do respond (Sarrabayrouse et al. 2014). Moreover, DP8α T cells exhibit a regulatory phenotype *in vitro* (Sarrabayrouse et al. 2014, Godefroy et al. 2018, Alameddine et al. 2019) and dampen colitis severity in mice when combined with the administration of *Faecalibacterium* (Touch et al. 2022). IBD is also characterized by elevated levels of IgG antibodies in the mucus and serum. In a study where fecal samples from healthy individuals and IBD patients were incubated with autologous serum, the IgG-coated fractions from IBD patients displayed a lower-level response to *Faecalibacterium*. Thus, IBD patients displayed a higher relative level of immunological tolerance to this genus compared to other genera, including *Streptococcus*, *Lactobacillus*, and *Lactococcus* (Bourgonje et al. 2022).

Specific phages can infect *Faecalibacterium* and may play a role in several human diseases, including IBD (Cornuault et al. 2018). *Faecalibacterium* phages occur at higher levels in feces from humans with IBD than in feces from healthy controls (Cornuault et al. 2018). Such could partially explain the decline in bacterial abundance, along with redox imbalance during inflammation. In mice, treatments using *Faecalibacterium* or supernatant from *Faecalibacterium* cultures decreased inflammation severity in several murine models for colitis (Sokol et al. 2008, Carlsson et al. 2013, Qiu et al. 2013, Martin et al. 2014, Laval et al. 2015).

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a commonly occurring gastrointestinal disorder characterized by altered bowel habits, chronic abdominal pain, the absence of detectable structural abnormalities in the colon, and increased gut permeability (Marshall et al. 2004). Although less is known about the relationship between the microbiota and IBS than in the case of IBD, abnormalities in fecal microbiota have been found in a subgroup of IBS patients who experienced bloating, as well as altered intestinal motility or sensitivity (Collins et al. 2009). Furthermore, dysbiosis has been observed in at least some subsets of IBS (Bonfrate et al. 2013, Bennet et al. 2015, Sabo and Dumitrascu 2021, Chen et al. 2023). More specifically, individuals with alternating-type IBS (IBS-A) have significantly lower levels of *Faecalibacterium*. In contrast, *Faecalibacterium* abundance is unaltered in individuals with diarrhea-predominant IBS (IBS-D) and is either notably lower or unaltered in individuals with constipation-predominant IBS (IBS-C) (Rajilic-Stojanovic et al. 2011, Duboc et al. 2012, Rigsbee et al. 2012). In a recent study using multicenter amplicon sequencing data, Chen et al. (2023) found that, within a cohort of 708 individuals (354 IBS patients and 354 healthy controls), the genus *Faecalibacterium* was one of the depleted taxa in IBS patients. The same study showed that *Faecalibacterium* was among the top 10 hub taxa in all the IBS subtypes identified by co-occurrence network analysis and was also among the top three genera identified as potential microbial biomarkers for IBS using a random forest model (alongside *Pseudoclostridium* and *Bifidobacterium*) (Chen et al. 2023). Furthermore, a negative correlation has been observed between *Faecalibacterium* abundance and IBS severity in humans (Rajilic-Stojanovic et al. 2011). In murine models of visceral pain mimicking IBS, such as those using neonatal maternal separation (NMS) and partial restraint stress (PRS), hypersensitivity decreased in response to supplementation with *F. duncaniae* A2-165 bacteria (but not supernatant) (Miquel et al. 2016). Given that low-grade inflammation has been reported in a subset of human IBS patients (Collins 1992,

Akiho et al. 2010), treatments using the A2-165 strain could possibly produce benefits because of the anti-inflammatory properties the bacterium displays. However, evidence for this hypothesis remains unclear given that, while both *F. duncaniae* A2-165 and its supernatant helped counteract impairment of the intestinal epithelial barrier in a murine model of chronic low-grade inflammation, only the bacterium was effective in murine models of NMS and PRS, indicating that other mechanisms likely explain the observed beneficial effects in mice (Martin et al. 2015).

Obesity, metabolic conditions, and liver disorders

Abnormal or excessive fat accumulation can present health risks. The Obesity Medicine Association defines obesity as 'a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences'. Obesity is associated with health concerns such as type 2 diabetes (T2D), hypertension, and cancer (Arroyo-Johnson and Mincey 2016).

Obese or T2D patients have lower microbiota diversity, and *Faecalibacterium* is one of the community members that has been found to differ (Le Chatellier et al. 2013). These results were corroborated by an Iranian study, which observed a negative correlation between *Faecalibacterium* levels and BMI (Navab-Moghadam et al. 2017). Chinese T2D patients displayed reduced abundances of *Bacteroides*, *Akkermansia*, and *Faecalibacterium*. Evidence of this shift was even detectable in prediabetic obese patients, reflecting the link between glucose intolerance and microbiota composition (Zhang et al. 2013). In other research, *Faecalibacterium* was enriched in T2D patients following weight loss (Hippe et al. 2016). Intriguingly, the same study found that samples from lean patients contained higher numbers of *Faecalibacterium* genes than did samples from obese and T2D patients; in contrast, lean patients had the lowest number of copies of the *Faecalibacterium*–associated butyryl-CoA:acetate CoA-transferase (BUT) gene. T2D patients had the highest butyrate levels. These findings could be interpreted as indicating that different *Faecalibacterium* species produce different levels of butyrate *in vivo* and that the taxon's abundance varies between healthy and unhealthy individuals (Hippe et al. 2016). Consequently, although the exact mechanisms have yet to be determined, current research supports a relationship between BMI, blood glucose levels, and *Faecalibacterium* abundance. In mice, supplementation with *F. duncaniae* A2-165 bacteria holds promise for treating obesity and its related complications. Compared to control mice, HFD-fed mice given twice-weekly supplements of *F. duncaniae* A2-165 had smaller adipocytes as well as reduced hepatic inflammation, lipid accumulation in the liver, and inflammatory cell infiltration in adipose tissue (Munukka et al. 2017). While these results seem quite promising, studies on obesity in mice not always translate to humans and must, therefore, be carefully interpreted and validated by clinical intervention-based trials in humans.

In preliminary research, lower levels of *Faecalibacterium* were also observed in individuals with rare metabolic diseases such as propionic acidemia (Tims et al. 2022), phenylketonuria (Verduci et al. 2018), or glycogen storage disease type 1 (Ceccarani et al. 2020). Finally, patients with liver cirrhosis showed reduced amounts of certain *Faecalibacterium* phylogroups, especially those that are better butyrate producers (Chen et al. 2021). More research should be performed to clarify the significance of these observations.

Neurological conditions

The gut microbiota plays an important role in the complex crosstalk that takes place between the gut and the brain (Alonso-García et al. 2021). Thus, it is unsurprising that microbial dysbiosis has been observed in individuals with a range of neurological conditions, opening the door to research on the microbiota–gut–brain axis (Cryan et al. 2019). In addition, several neurological conditions have been associated with leaky gut syndrome and a proinflammatory shift in the colonic microbiota, which results from increased levels of Gram-negative bacteria containing immune-triggering lipopolysaccharides (LPSs) (Eicher and Mohajeri 2022). Correlations have also been found with lower abundances of *Bifidobacterium*, *Coprococccus*, *Eubacterium*, *Lactobacillus*, *Prevotella*, *Roseburia*, and *Faecalibacterium* (Eicher and Mohajeri 2022). The latter genus has been found to occur at lower levels in individuals with clinical depression (Ye et al. 2021). Exploratory studies have observed similar patterns in association with several additional psychiatric conditions, including bipolar disorder, anxiety, psychosis, and schizophrenia (Nikolova et al. 2021).

Alterations in gut microbiota have also been seen in proteinopathies such as Parkinson's disease (PD) and Alzheimer's disease (AD) (Nishiwaki et al. 2020, Xi et al. 2021). For example, *Faecalibacterium* levels were found to be lower in PD patients than in healthy controls (Nishiwaki et al. 2020). Recently, *Faecalibacterium* strains isolated from healthy human donors were tested in a murine model of AD; the administration of both living and dead bacteria improved cognitive impairment (Ueda et al. 2021). Furthermore, *Faecalibacterium* abundance was found to be higher in healthy individuals than in individuals with mild cognitive impairment (MCI) and AD patients, in whom it was positively correlated with cognitive performance (Ueda et al. 2021).

Recent preliminary research found that children on the autism spectrum had higher levels of *Faecalibacterium* (Xu et al. 2019, Iglesias-Vazquez et al. 2020). Unexpectedly, an intervention study discovered that autistic children who consumed gluten- and casein-restricted diets were better able to handle autism-related behavioral challenges and had higher *Faecalibacterium* levels than autistic children who consumed the control diet (Grimaldi et al. 2018). Members of this genus were found to be more abundant in individuals with epilepsy, although there were no links with severity status (Valles-Colomer et al. 2019, Cui et al. 2021).

Intriguing results aside, these results should be interpreted with caution because research relating *Faecalibacterium* abundance to neurological conditions is far more preliminary than that examining the links with diseases such as IBD.

Cancer

The gut microbiota also appears to have an impact on the efficacy of immune checkpoint inhibitors (Routy et al. 2018, Daillere et al. 2020, Effendi et al. 2022). Indeed, several studies have shown that a higher baseline level of *Faecalibacterium*, as well as that of other Firmicutes, positively correlates with responses to related treatments for various cancers, such as melanoma (Chaput et al. 2017, Gopalakrishnan et al. 2018, Coutzac et al. 2020, Limeta et al. 2020, Spencer et al. 2021), hepatocellular carcinoma (Li and Ye 2020), and nonsmall cell lung cancer (Newsome et al. 2022).

In a rat model where colorectal cancer (CRC) was induced via azoxymethane (AOM), treatment with *F. prausnitzii* reduced disease markers as well as lipid peroxidation (Dikeocha et al. 2022). Indeed, Kenyan patients with CRC were found to have intestinal mucosa-associated microbiota and microbial metabolic profiles different from those of healthy individuals (Obuya et al.

2022). In particular, *Prevotella copri* and *Faecalibacterium* species were less abundant, and alterations were observed in glutamate metabolism.

In another study, breast cancer patients showed reduced fecal levels of *Faecalibacterium* (Ma et al. 2020). Moreover, when *Faecalibacterium* and MCF-7 breast cancer cells were cocultured *in vitro*, proliferation of the latter was hampered through the inhibition of IL-6 production and the phosphorylation of JAK2/signal transducers and STAT3 activators (Ma et al. 2020). Interestingly, a recent study demonstrated that a mixture of four commensal Clostridiales strains (i.e. CC4: *F. prausnitzii*, *R. intestinalis*, *Eubacterium hallii*, and *Anaerostipes caccae*) displayed anticarcinogenic properties against different solid tumors (Montalban-Arques et al. 2021). The rationale behind CC4 composition was to combine different commensal strains capable of producing butyrate. In another preclinical rat model, treatment with *F. duncaniae* helped repair collateral damage in the colon that was caused by radiation therapy, a common treatment for cancer in the pelvic area. Mechanistically, this effect arose from reductions in hyperpermeability and neutrophil infiltration; the preservation of progenitor cells and colon cell morphology; and the upregulation of IL-18 expression (Lapiere et al. 2020).

Dermatitis and allergies

Atopic dermatitis is a condition in which the skin is chronically inflammed, resulting in redness, dryness, and irritation. It is characterized by a reduction in skin microbiota diversity, which facilitates colonization by pathogenic bacteria, such as *Staphylococcus aureus*, leading to increased disease severity (Paller et al. 2019). Gut dynamics in early childhood might have an important role to play. Indeed, metabolites production by some types of bacteria, from infancy to adulthood, results in heightened immune system priming and contributes to atopic dermatitis development, which means that early life experiences are likely key contributors to this condition (Gensollen and Blumberg 2017). Research has also shown that atopic dermatitis is associated with shifts in the gut microbiota. In a study conducted using 42 healthy individuals and 30 individuals with the condition, the latter had reduced butyrate and propionate levels in their feces; furthermore, they had lower abundances of *Faecalibacterium* subspecies related exclusively to *F. duncaniae* A2-165 (Song et al. 2016, Effendi et al. 2022). *Faecalibacterium* levels are reduced in individuals with psoriasis, but not in those with hidradenitis suppurativa, which can co-occur with IBD (Eppinga et al. 2016). Surprisingly, in a murine wound healing model, i.e. commonly employed to study healing dynamics and treatment efficacity, treatment with supernatant from *Faecalibacterium* cultures improved several types of skin lesions caused by intense, sustained inflammation, such as ulcers (Stefia et al. 2020). In NC/Nga mice in which atopic dermatitis had been induced using 2,5-dinitrochlorobencene (DNCB), the administration of *Faecalibacterium* improved symptoms by boosting the Th2 response, thus counterbalancing the excessive Th1 response elicited in the model (Lee et al. 2022). These promising results remain to be validated by clinical trials with humans.

Asthma is a chronic inflammatory condition that impacts lung airways. Research has suggested that shifts in the gut microbiome can impact the outcome of lung diseases. Indeed, the higher prevalence of lung diseases in individuals with gastrointestinal disorders supports the existence of a gut–lung axis, of which SCFAs may be major drivers (Correa et al. 2022). While findings for adults remain inconclusive (Wang et al. 2018b, Tikunov et al. 2021), children with allergic asthma had lower *Faecalibacterium* levels than did healthy children (Demirci et al. 2019). Finally, in a murine model, both living and dead *F. duncaniae* were able to alleviate dust mite-induced allergic asthma by modulating the microbiota and increasing butyrate production, an interesting finding that should be explored in future research (Hu et al. 2021).

Covid-19

Infection with SARS-CoV-2 causes the disease COVID-19, which mainly affects the respiratory system. Although COVID-19 commonly causes fever and respiratory tract symptoms, it may also lead to cardiac, gastrointestinal, hepatic, renal, neurological, olfactory, gustatory, ocular, cutaneous, and hematological symptoms (Zhang and Guo 2020). SARS-CoV-2 affects the gastrointestinal system because the virus enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is abundantly present on the glandular cells of the gastric, duodenal, and rectal epithelia as well as on the endothelial cells of the small intestine (Zhang and Guo 2020). Thus, the virus can also infect enterocytes, as revealed by the presence of viral RNA in feces (Trottein and Sokol 2020, Yeoh et al. 2021). Furthermore, several studies have described a pattern of infection-related dysbiosis, i.e. marked by a reduction in *Faecalibacterium* abundance, particularly in hospitalized patients with the severe phenotype (Yeoh et al. 2021, Hazan et al. 2022). Additionally, individuals suffering from postacute COVID-19 syndrome (PACS), otherwise known as Long COVID, have higher levels of *Ruminococcus gnavus* and *Bacteroides vulgatus* and lower levels of *Faecalibacterium* (Liu et al. 2022). Since *Faecalibacterium* holds promise for treating the intestinal issues caused by other gut-related disorders, its use has been proposed to help relieve COVID-19-related symptoms (He et al. 2021). Indeed, COVID-19 patients that received a fecal microbiota transfer (FMT) had higher levels of *Faecalibacterium* following the procedure than during the course of their infection (Liu et al. 2021). Moreover, in a preclinical model in hamsters, the oral administration of a *Faecalibacterium* strain to SARS-CoV-2 infected animals resulted in a 10-fold reduction in viral load (Monchatre-Leroy et al. 2021).

Host-*Faecalibacterium* cross-talk

Beneficial effects on the host

Several studies have sought to decipher how *Faecalibacterium* presence promotes GIT homeostasis using *in vivo* murine models or *in vitro* testing with human cell lines. Numerous types of evidence suggest that this genus plays an important role in immune system regulation, gut barrier protection, and microbiota modulation (Miquel et al. 2013), potentially via a range of mechanisms (Fig. 5). However, it is important to note that research on the interactions between *Faecalibacterium* and their hosts is in constant flux for two reasons. First, the taxonomy of the genus is undergoing shifts because of new discoveries. Second, it is difficult to separate out general effects, potentially attributable to multiple butyrate-producing bacteria, from effects specific to *Faecalibacterium*. Some studies have shown that the presence of specific species can modulate the host immune system, by upregulating IL-10 expression in dendritic cells and enhancing the proliferation of T cells, which suggests the presence of an effect specific to *Faecalibacterium* (Rossi et al. 2016). In support of this idea, *in vitro* tests revealed that the presence of different clinical isolates led to the upregulation of IL-10 in the human peripheral blood mononuclear cells (PBMCs) of healthy individuals; this result was seen especially, but not exclusively, in association with bacteria displaying higher levels of butyrate production (Martin et al. 2017). The presence of these

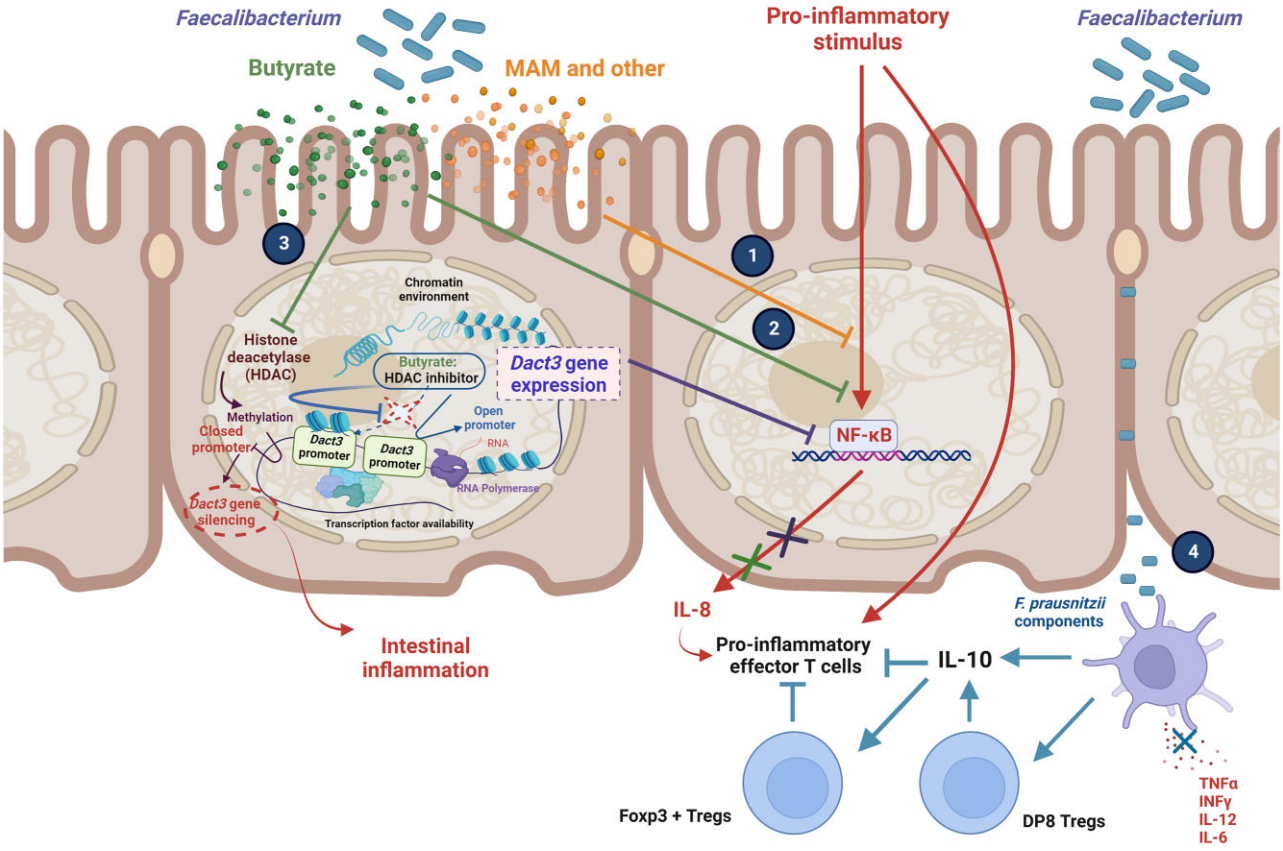

Figure 5. Mechanisms of action associated with *Faecalibacterium*. (1) Supernatant from *Faecalibacterium* cultures blocks the activation of NF-κB induced by a proinflammatory stimulus. (2) Butyrate produced by *Faecalibaterium* inhibits NF-κB activation and blocks Il-8 production in TNF-α stimulated intestinal epithelial cells. (3) Butyrate inhibits HDAC, leading to the expression of *Dact3*, a gene encoding a negative regulator of the inflammatory Wnt/JNK signaling pathway, and the inhibition of IL-8 production. It is important to note that the silencing of *Dact3* leads to a partial loss of the anti-inflammatory effects of *Faecalibacterium* supernatant in the intestinal epithelial cells. (4) *Faecalibaterium* components can induce the appearance of a specific subset of IL-10-secreting Treg cells—called DP8 cells—in the colonic lamina propria. Moreover, the presence of *Faecalibacterium* can boost IL-10 levels in antigen-presenting cells and DP8 cells, which may enhance the suppressive activity of Foxp3 + Treg cells and block proinflammatory effector T cells induced by various stimuli.

clinical isolates could also block IL-8 production in human HT-29 cells that had been activated with TNF–α, although, in this model, there was no clear genus-specific effect tied to butyrate production (Martin et al. 2017). Additionally, treatment with *F. duncaniae* has been shown to increase levels of a specific subset of IL-10-secreting Treg cells (CD4CD8α) in the *lamina propria* of the colon; these cells are lacking in individuals with IBD. In a humanized murine model, the administration of DP8α cells and *F. duncaniae* protected against dextran sulfate sodium (DSS)-induced colitis induced (Touch et al. 2022). However, it is not yet known whether this effect is species-specific.

Faecalibacterium presence can also affect intestinal epithelial cells. In assays using human Caco-2 cells, IL-1β-induced NF-κB activity was abolished after the addition of supernatant from *Faecalibacterium* cultures but not after the addition of *Faecalibacterium* cells (Sokol et al. 2008). Furthermore, in a murine model where colitis was induced using dinitrobenzene sulfonic acid (DNBS), the butyrate produced by *Faecalibacterium* upregulated expression of the *dishevelled binding antagonist of beta catenin 3* (*Dact3*) gene in TNFα–stimulated HT-29 cells (Lenoir et al. 2020). Dact3 is a negative regulator of the inflammatory Wnt/JNK signaling pathway and could be one of the host effectors that mediates the positive effects attributed to *Faecalibacterium*, given that its silencing leads to a partial loss of supernatant-mediated anti-inflammatory effects in intestinal epithelial cells. That said, the key role played by butyrate makes difficult to determine whether the presence of *Faecalibacterium* specifically contributes to activation (Lenoir et al. 2020).

The presence of *Faecalibacterium* also appears to have impacts on the intestinal barrier. Treatment with *F. duncaniae* A2-165 was found to improve gut permeability and function in a murine model of DNBS-induced intestinal barrier impairment (Sokol et al. 2008, Martin et al. 2014, Laval et al. 2015, Martin et al. 2015, Miquel et al. 2015a). Rossi et al. (2015, 2016) and Carlsson et al. (2013) also found that treatment helped restore intestinal permability in a model of DSS-induced colitis in mice. In all these cases, it is difficult to distinguish whether these beneficial effects arise from the anti-inflammatory properties of the bacteria or the physical effects of the bacteria on the barrier. However, in a noninflammatory model of gut alteration in mice, administration of *F. duncaniae* A2-165 led to the recovery of claudin-2 levels, which had been altered using NMS (Miquel et al. 2016). It also ameliorated the degree of radiation-induced colonic hyperpermeability by preserving the progenitor cells and colon cell morphology in mice (Lapiere et al. 2020). In a nonpathological model using germ-free rats colonized by *B. thetaiotaomicron* and *F. duncaniae* A2-165, the presence of the latter diminished the negative effects of *Bacteroides* on goblet cell differentiation and mucin glycosylation. This effect likely stems from the strain's metabolic processes, in which acetate is consumed and butyrate is produced, and underscores how the

presence of *Faecalibacterium* helps modulate the gut microbial community during host–microbiome interactions (Wrzosek et al. 2013).

Bacterial effectors

Metabolites

As mentioned previously, one of the main metabolites produced by *Faecalibacterium* is butyrate (Duncan et al. 2004), which has several effects on host physiology. For example, it can be used by colonocytes as a carbon source and bolster the gut barrier by strengthening the tight junctions (Liu et al. 2018). In continuous cocultures with primary epithelial cells, butyrate production by *F. duncaniae* A2-15 was correlated with the downregulation of TLR3 and TLR4 expression via the HDAC1 and NF-kB pathways (Zhang et al. 2021). The health effects of butyrate are reviewed elsewhere (Liu et al. 2018).

In a gnotobiotic model employing *F. duncaniae* A2-165 and *E. coli*, metabolomic analysis identified several metabolites—including salicylic acid, shikimic acid, and raffinose—that could play a role in the benefits attributed to the bacterium (Miquel et al. 2015b). Some studies have suggested that salicylic acid could help treat obesity, by inducing the browning of white adipocytes (Choi et al. 2022), or could serve as a preventive treatment for CRC (Imai et al. 2022). Furthermore, it is used as a coadjuvant in cancer treatments because it can boost the effects of antitumor immunotherapy (Sun et al. 2022). In the pharmaceutical industry, salicylic acid is used to produce the amine derivative 5-aminosalicylic acid (5-ASA or mesalamine), currently used to treat IBD (Messori et al. 1994). The effects of aspirin might be mediated via its transformation into salicylic acid, a process that can be carried out by members of the gut microbiota (Zhao et al. 2020). Through the achorismate synthase pathway, shikimic acid acts as a precursor for the synthesis of several aromatic compounds, including salicylic acid (Bochkov et al. 2012). Consequently, *F. duncaniae* may play a key role in the biosynthesis of salicylic acid, which is a precursor of 5-ASA. Both are anti-inflammatory molecules that could contribute to the anti-inflammatory effects observed *in vivo* in mice treated with *Faecalibacterium*. In addition, the oligosaccharide raffinose is a potential effector that could serve to address intestinal barrier dysfunction induced by *Faecalibacterium* presence during inflammation (Martin et al. 2018). It has yet to be determined whether *Faecalibacterium* produces these three metabolites, or if they are produced by host cells when *Faecalibacterium* is present.

Finally, we have also identified the butyrate as the *F. prausnitzii* effector responsible for Dact3 modulation (see the section 'Beneficial effects on the host'). The elucidation of the impact of *F. prausnitzii* is Dact3 upregulation validated *in vivo* in both healthy and inflamed mice is currently in progress.

Extracellular vesicles

Extracellular vesicles (EVs) are spherical membranous vesicles used by prokaryotic and eukaryotic cells to release compounds into the extracellular space for functional reasons, such as responding to environmental changes or communicating with the host or other bacteria (Deatherage and Cookson 2012). Recent work has underscored that EVs could potentially serve as biomarkers or therapeutic tools, which has resulted in an increase in the number of EV-focused studies. EVs are released by all cellular organisms, including Gram-positive bacteria (Toyofuku et al. 2023), and, since they were first described, unexpected biophysical, biochemical, and functional heterogeneity has been observed (Buzas 2023). For *F. duncaniae* A2-165, EVs were first isolated and characterized by Jafari et al. in 2019. The EVs contain proteins ranging in size from 11 to 245 kDa (Jafari et al. 2019). In Caco-2 cells, a treatment utilizing EVs from A2-165 and *A. municiphila* augmented serotonin production and the expression of genes related to serotonin (Yaghoubfar et al. 2021). Similarly, the EVs alone strengthened the expression of genes encoding tight junction proteins [zonula occludens 1 (ZO1) and occludin (OCLN)] and ParR family compounds, results that confirm the role of EVs in maintaining gut barrier integrity (Moosavi et al. 2020). EVs from *Faecalibacterium* species are also involved in immune homeostasis: when used to treat Caco-2 cells, they significantly diminished levels of several proinflammatory cytokines (Rabiei et al. 2019). Similar results were obtained in a model utilizing *Faecalibacterium* EVs and the lung cancer cell line A549 (Jafari et al. 2019). Taken together, these results should encourage further research on the potential role played by *Faecalibacterium* EVs in hosts and drive additional, more conclusive research in this field.

Microbial anti-inflammatory molecule

The microbial anti-inflammatory molecule (MAM; ZP05614546.1) is 15 kDa in size and has a nonpolar residue prevalence of 53%. It was first described in a peptidomic analysis of supernatants from *Faecalibacterium* cultures, in which seven of its derivative peptides inhibited the NF-kB pathway in intestinal epithelial cells, displaying the potential for anti-inflammatory effects (Quevrain et al. 2016). Indeed, in DNBS and DSS models employing NF-κ–luciferase transgenic mice, a decrease in proinflammatory cytokines related to Th1 and Th17 responses was observed in mice gavaged with *Lactococcus lactis* strain delivering MAM cDNA (Breyner et al. 2017). Recent *in vitro* and *in vivo* studies have shown that MAM's anti-inflammatory properties are diverse and species-specific. In murine models of DNBS-induced acute and chronic inflammation, the MAM from the *F. prausnitzii* strain M21-2 was more effective than the MAM from *F. duncaniae* A2-165 (Auger et al. 2022).

The effects of MAM were examined in db/db mice, which do not express leptin receptors and have lower levels of *Faecalibacterium* in their guts. Oral supplementation with *E. coli*-produced MAM suggest that the molecule interacts with ZO-1 and other tight junction proteins. Furthermore, the transfection of MAM into a cell line increased ZO-1 expression and restored epithelial barrier function (Xu et al. 2019). These results suggest that MAM has therapeutic potential in improving intestinal barrier function.

Extracellular polymeric matrix

The presence of a biofilm-forming strain, *Faecalibacterium* HTF-F, inhibited the production of proinflammatory signals in human dendritic cells that had been stimulated using *L. plantarum*. In the same study, the presence of the HTF-F strain was better than the presence of the A2-165 strain at improving symptoms of DSS-induced colitis (Rossi et al. 2015). The authors concluded that the greater anti-inflammatory effects associated with HTF-F could be related to the extracellular polymeric matrix (EPM) of the strain's biofilm. However, given ongoing taxonomic shifts within *Faecalibacterium*, it is essential to carefully explore other differences between these two strains, which belong to different phylogenetic cluster.

Faecalibacterium as a therapeutic tool

Potential applications

In the last 15 years, the field of probiotics has exploded as a result of massive leaps in knowledge about the gut microbiota and its crucial role in human health. Probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit to the host' (Hill et al. 2014). They are usually microor-

ganisms and most frequently a specific list of bacterial genera of proven safety with a long history of use in mainly healthy people (Martin and Langella 2019). However, this more classical definition of probiotics has evolved over time to include next-generation probiotics (NGPs) and live biotherapeutic products (LBPs). In contrast to conventional probiotics, these two new groups do not have an established history of safe use in humans. Instead, NGPs and LBPs are directly isolated from the human gut microbiome and then carefully chosen for their biological effects. *Faecalibacterium* holds great promise as an LBP because of its demonstrated role in host homeostasis and its many positive effects in preclinical murine models for various diseases (e.g. IBD, CRC, AD, and even radiation therapy). Its use is already being explored in livestock. For instance, research has characterized *Faecalibacterum* strains isolated from the stool of calves and piglets (Foditsch et al. 2014). Given the strong relationship between IBD in humans and lower levels of *Faecalibacterium* (Sokol et al. 2008, 2009, Cao et al. 2014), the genus is clearly a potential LBP candidate. It is being used for the first time in a clinical trial focused on maintaining both corticosteroid-induced clinical responses and remission in individuals with CD (MAINTAIN 2022). This phase 1 study has two parts: a open-label evaluation of safety using a small group of participants and a randomised, double-blind, placebo-controlled evaluation using a large group of participants (ClinicalTrials.gov Identifier: NCT05542355). Furthermore, a specific formulation has been proposed to keep these EOS bacteria alive under ambient conditions, which would be necessary to treat patients with intestinal dysbiosis-associated diseases (Khan et al. 2014).

Additionally, *Faecalibacterium* could serve as an effective disease biomarker and diagnostic support tool (Miquel et al. 2013). In 2008, a diagnostic test based on *Faecalibacterium* prevalence and leukocyte counts was developed to distinguish active CD from UC and displayed a high level of performance (79%–80% sensitivity and 98%–100% specificity) (Swidsinski et al. 2008). As-yet-undiscovered species and phylotypes could yield further insights and improve the accuracy of methods that utilize *Faecalibacterium* as a disease marker. Work addressing these issues is especially important since different ratios of strains and phylotypes have been seen in association with several health conditions, such as AD and obesity (Lopez-Siles et al. 2017).

Interventions to modulate faecalibacterium

Dietary interventions, including probiotics and prebiotics

Dietary interventions remain one of the most efficient ways for modifying the microbiota. For example, eating the fiber-rich Mediterranean diet can result in higher levels of *Faecalibacterium* (Godny et al. 2022). Several studies have investigated nutritional strategies for increasing the abundance of this genus in the gut. A 30-day diet of the alga *Euglena gracilis* was observed to increase *Faecalibacterium* levels (Nakashima et al. 2021). The same effect was achieved via a 6-day, lifestyle-based immersion program that included nutritional intervention: with 100% plant based meals and that incorporated whole foods (Ahrens et al. 2021). Similarly, levels of *Faecalibacterium* increased in children given a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), and the abundance of bacteria in this taxon correlated with symptom improvement (Chumpitazi et al. 2015). The FODMAP diet contains reduced quantities of fermentable carbohydrates and has been effective in reducing gastrointestinal symptoms in adults with IBD and IBS, even if it decreases *Faecalibacterium* levels (Hustoft et al. 2017, Cox et al. 2020). However, it remains unclear whether the relationship between this diet and *Faecalibacterium* abundance is consistent, an issue discussed in a recent systematic review (Vandeputte and Joossens 2020). In a 6-month controlled-feeding experiment, 217 healthy young adults were randomly assigned a low-, mid-, or high-fat diet; those consuming the low-fat diet showed a decrease in *Faecalibacterium* levels (Wan et al. 2019). In contrast, no such changes were seen during a 3-month single-center intervention where six patients with glucose transporter 1 deficiency syndrome were given a traditional ketogenic diet (i.e. high fat and low carbohydrate) (Tagliabue et al. 2017). Several studies in rodents have revealed the existence of a negative correlation between protein intake and *Faecalibacterium* abundance, as noted in a systematic review of how dietary proteins affect the gut microbiota (Wu et al. 2022). Research examining this relationship remains scarce, and few intervention studies have been conducted using healthy subjects. Finally, fasting has been found to increase *Faecalibacterium* levels in humans, confirming that dietary habits may shape *Faecalibacterium* occurrence in myriad ways (Remely et al. 2015).

Prebiotics are another tool that can be used to modulate the levels of *Faecalibacterium*. A prebiotic is a 'non-digestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host' (Bindels et al. 2015). *Faecalibacterium* is a fibre fermenter, and several studies have found a positive correlation between levels of dietary fibre and the relative abundance of this genus (Benus et al. 2010). Historically, supplementation with inulin was one of the first strategies successfully used to increase the representation of *Faecalibacterium* within the microbial community of the human gut (Ramirez-Farias et al. 2009). A recent systematic review has highlighted the ability of prebiotics to boost *Faecalibacterium* abundance (Verhoog et al. 2019). Indeed, in germ-free mice conventionalized with human microbiota, the administration of a supplement containing resistant starch increased butyrate production and increased *Faecalibacterium* levels; the effect was more substantial when donors had lower initial abundances of the genus (Cherbuy et al. 2019). In a randomized placebo-controlled crossover study, the intake of polydextrose and soluble corn fiber boosted levels of *Faecalibacterium* (Hooda et al. 2012). In another crossover study, the consumption of chickpea and its main oligosaccharide, raffinose, had the same effect (Fernando et al. 2010).

It has been hypothesized that traditional probiotics can help treat disease-related bacterial imbalances in the gut microbiome. Some improve *Faecalibacterium* abundance, perhaps because traditional probiotics often produce acetate. Acetate promotes the growth of *Faecalibacterium* via cross-feeding (Ramirez-Farias et al. 2009). For instance, during a dietary intervention study that used *L. plantarum* PMO08, *Faecalibacterium* levels had significantly increased after 2 weeks of treatment (Oh et al. 2021). Host health improved and *Faecalibacterium* abundance increased in response to the administration of *L. plantarum* ZPL001, *Enterococcus durans* EP1, and *L. paracasei* N1115, among others (Carasi et al. 2017, Wang et al. 2018a).

Medications

It is well-established that antibiotics greatly impact the structural composition of the gut microbiota (Wang et al. 2023). For example, an 8-week amoxicillin treatment led to diminished levels of *Faecalibaterium* (Pallav et al. 2014), as did the administration of ciprofloxacin (Stewardson et al. 2015). In contrast, nitrofurantoin, a medication mainly used for urinary tract infections, increased the abundance of four genera of Firmicutes, including that of *Faecalibacterium* (Stewardson et al. 2015). In vaginal-delivered in-

fants, *Faecalibacterium* levels were lower at the 1-year mark for babies that had received postnatal antibiotics at any point compared to babies that had not (Ainonen et al. 2022). Another study reported that antibiotic and antifungal treatments diminished *Faecalibacterium* abundance in children with leukemia (Dunn et al. 2022); the same result was seen in response to intraveinously administered antibiotics in individuals with multiple myeloma (D'Angelo et al. 2022).

Shifts in *Faecalibacterium* levels have also been observed following exposure to other drugs. For example, they have been seen to decline in individuals taking diabetes medications including metformine (Manor et al. 2020) or to display partial restoration in those taking vortioxetine for depression (Ye et al. 2021). In contrast, a cross-sectional study in humans (n = 8583 participants) found no significant correlations between *Faecalibacterium* abundance and levels of different drug metabolites in the blood (Dekkers et al. 2022).

Fecal microbiota transplants

Fecal microbiota transplants have been extensively used to deal with multirecurrent *Clostridioides difficile* infections (CDIs), and their use in other contexts is currently under exploration (Cammarota et al. 2017). *Faecalibacterium* levels have been found decreased in patients with CDIs and low levels of *Faecalibacterium* are proposed as predictive of CDIs recurrence (Han et al. 2020, Khanna et al. 2016, Lee et al. 2020, Milani et al. 2016, Stewart et al. 2019). Research indicates that fecal microbiota transplants could restore and maintain *Faecalibacterium* levels for 2–4 months (Bjorkqvist et al. 2021). Indeed, in a case study of coinfection with *C. difficile* and an extensively drug-resistant KPC-producing *Klebsiella pneumoniae*, the levels of *Faecalibacterium* increased after the fecal microbiota transplant (Bahl et al. 2020). In a murine model, transplants led to the recovery of *Faecalibacterium* levels that had diminished following treatment with antibiotics and chemotherapy (Le Bastard et al. 2018), confirming the promise of this strategy.

Technical and legislative challenges

Before EOS bacteria can be administered to human subjects, there is a 2-fold challenge to resolve: (1) bacteria need to be produced at large scales in the absence of animal compounds and under strictly anaerobic conditions and (2) sufficiently anoxic conditions must be maintained across all the postculture processing steps (e.g. centrifugation, filtration, or lyophilization). In addition, the bacteria should remain alive during storage, so as to reach the gut in an effective state. *Faecalibacterium* is not only EOS. It is also highly sensitive to slight increases (from 0.1% to 0.5%) in physiological concentrations of bile salts, and its optimal pH is between 5.7 and 6.7 (Lopez-Siles et al. 2012, Lopez-Siles et al. 2017). To solve this problem, *Faecalibacterium* could be encapsulated so that it could survive transit through the GIT (Raise et al. 2020). To further simplify this part of the process, nonviable bacteria could be employed. A recent study compared the preventive and therapeutic effects of administering live vs. inactivated *F. prausnitzii* ATCC27768 in murine models of DSS-induced colitis (Kawade et al. 2019). It was found that mice given live *F. prausnitzii* recovered better than did mice given inactivated *F. prausnitzii* (Kawade et al. 2019). That said, dead bacteria were effective in a murine model of AD (i.e. improved AD-related cognitive impairment) and in a murine model of allergic asthma (Hu et al. 2021, Ueda et al. 2021). To address this question more clearly, we need additional research that focuses on direct crosstalk between *Faecalibacterium* and the host. Furthermore, the efficacy of live versus dead bacteria could depend on design variables, including the strain or model employed, or various technical variables. To provide clarity, more research should be conducted on the mechanisms by which dead bacteria could have impacts.

As stated above, probiotic therapy often seeks to restore balance of the intestinal ecosystem. This objective could be achieved with naturally occurring commensal bacteria in the form of NGPs or LBPs (Miquel et al. 2015a). However, unlike traditional probiotic strains, these bacteria are not recognized under formal product safety regimes in either Europe [qualified presumption of safety (QPS)] or the USA [generally recognized as safe (GRAS)]. Furthermore, as they have a short track record of safe consumption—no safe use was documented in Europe prior to 1997—these NGPs must be treated as novel foods or drugs, and they will face more severe commercial requirements in Europe than their conventional counterparts did (Miquel et al. 2015b). Although *Faecalibacterium* is not on the QPS list as most of the commensal bacteria, it holds great promise as a safe treatment given that thousands of FMTs have been performed worldwide without any *Faecalibacterium*-induced side effects or infections occurring. Moreover, regulatory agencies in Europe and the USA have already given the green light for research on how LBPs, including *Faecalibacterium*, affect humans (Cani 2018, CAUSALITY 2021, MAINTAIN 2022).

Conclusions and future perspectives

Ever since low levels of *Faecalibacterium* were discovered to be associated with several diseases, researchers have sought to characterize the mechanisms underlying interactions between hosts and members of this genus. In addition, as scientists have gained greater clarity around the taxonomy of *Faecalibacterium*, studies are being conducted in which the effects of the bacteria can be assigned to specific strains or species. In addition, a robust literature exists documenting the anti-inflammatory properties of the genus, in which the effects of butyrate, EVs, and cell wall components are addressed. Taken together, these findings have piqued interest in utilizing the genus as a LBP.

However, conclusions based on this work should be made with caution. First, most research to date has focused on the single strain *F. duncaniae* A2-165. Second, the beneficial effects have largely been observed in preclinical murine models. Third, the relationship between *Faecalibacterium* occurrence and diverse health conditions has been described based on correlational data, making it difficult to evaluate the degree to which *Faecalibacterium* has a causal effect on disease reduction. Clinical studies are currently underway to address these concerns, and they will play an important part in supporting the growing knowledge base being generated by preclinical and *in vitro* models.

Acknowledgements

The authors would like to thank all the people involved in gathering the knowledge that served as the basis for this review. In particular, we are grateful to our past and present colleagues who have demonstrated great dedication to this work: S. Miquel, M. Thomas, C. Bridonneau, S. Hudault, V. Robert, S. Chadi, F. Chain, N. Breyner, M. Lenoir, P. González-Dávila, D. Seda, L. Hua, P. Ruffié, S. Touch, N. Rolhion, L. Wrzosek, C. Cherbuy, P. Kharrak, C. Aubry, C. Michon, S. Verstraeten, J.J. Gratadoux, and S. Blugeon. L.B.G.H. is the recipient of an ANR grant (ANR-21-CE18-0050-01), and S.K. was paid a salary from this grant.

Conflict of interest statement: H.S. and P.L. are cofounders of the startup Exeliom Biosciences, whose objective is to generate an LBP based on *F. prausnitzii* that targets IBD. H.S. has received lecture fees, board membership compensation, or consultancy payments from Amgen, Fresenius, IPSEN, Actial, Astellas, Danone, THAC, Biose, BiomX, Eligo, Immusmol, Adare, Nestle, Ferring, MSD, Bledina, Pfizer, Biocodex, BMS, Bromatech, Gilead, Janssen, Mayoli, Roche, Sanofi, Servier, Takeda, or Abbvie and holds stocks issued by Enterome Biosciences. P.L. has received lecture fees, board membership compensation, or consultancy payments from Biose, Biostime, Boiron, Bonduelle, BMS, Bromatech, IPSEN, iTaK, Lallemand, Lesaffre, L'Oréal, Mayoli, Merck, Pilèje, Procter and Gamble, Second Genome, Therascience, and URGO.

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Received 5 January 2023; **revised** 8 June 2023; **accepted** 12 July 2023