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Overview

Segmented Filamentous Bacteria: Commensal Microbes with Potential Effects on Research

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Segmented filamentous bacteria (SFB) are commensal bacteria that were first identified in the ilea of mice and rats. Morphologically similar bacteria occur in a broad range of host species, but all strains have been refractory to in vitro culture thus far. Although SFB were once considered innocuous members of the intestinal microbiota of laboratory rodents, they are now known to affect the development of the immune system in rodents and, subsequently, the phenotype of models of both enteric and extraintestinal disease. Therefore, SFB represent long-recognized commensal bacteria serving as an intercurrent variable in studies using rodent models of disease. Here we describe the basic biology of SFB and discuss the immunologic and physiologic effects of colonization with SFB, with particular attention to their effects on rodent models of disease. In addition, we propose that SFB represent only the 'tip of the iceberg' in our understanding of the influence of the microbiota on model phenotypes. As next-generation sequencing techniques are increasingly used to investigate organisms that are refractory to culture, we are likely to identify other commensal microbes that alter the models we use. This review underscores the need to characterize such host–microbe interactions, given that animal research represents a critical tool that is particularly vulnerable to scrutiny in an era of decreasing financial resources and increasing accountability for the use of animal models.

Abbreviations: SFB, segmented filamentous bacteria; TLR, Toll-like receptor.

Almost half of a century ago, a few astute microscopists reported a unique microbe that remained securely attached to the epithelium of the ileum in mice (*Mus musculus*) and rats (*Rattus norvegicus*) despite the removal of other luminal contents.[32,69,71,72] Although the microbe was first postulated to be a fungus in light of its size and unusual morphology,[69] electron microscopy soon revealed the organism to be a segmented bacterium containing 'round forms,' some of which appeared to be in the process of dividing. In addition, one end of the microbe appeared to be specialized for integration into and attachment to the epithelial brush border. A very similar organism in the ileum of chickens (*Gallus domesticus*)[25] and dogs (*Canis familiaris*) was soon reported,[12] although the relationship among the microbes from the various hosts remained unclear. The first report of the habitat, ultrastructural morphology, and proposed life cycle of what are now commonly referred to as segmented filamentous bacteria (SFB) was published in 1974.[13] There are abundant anecdotal reports among users of animal models regarding the loss or alteration of model phenotypes when using animals purchased from different vendors or when housing animals under different husbandry conditions. These changes have often been attributed to genetic drift of rodent strains maintained at different institutions or to unknown factors of the host microbiota. Recent studies comparing mice from different vendors[19,37,38] have identified SFB as a pivotal member of the commensal microbiota that affects the ontogeny and function of the host immune system. Accordingly, what was once an incidental finding on histologic examination of the gastrointestinal tract should now be considered a variable with the potential to affect outcomes in several disease models. Identification of involved models and the extent to which they are affected is a critical need in biomedical research.

Unique Morphology

SFB are gram-positive, spore-forming, filamentous bacteria ranging between 0.7 and 1.8 µm in diameter and as long as 80 µm in length[10] that selectively colonize the ilea of mice and rats shortly before weaning[43,71] (Figure 1). The first segment of the microbe possesses a nipple-like appendage, called a holdfast, that projects into the plasma membrane of the enterocyte, without actually rupturing or penetrating the host cell wall[4,10,13,21,79] (Figure 2). It should be noted, however, that attachment of SFB induces focal displacement of the microvillar brush border and alterations in the electron-density of the enterocyte plasma membrane and apical cytoplasm. Actin polymerization occurs at the apical surface of enterocytes at the site of attachment,[40] suggesting pedestal formation, an active host cellular response similar to that induced by invasive or adherent pathogens such as *Escherichia coli*[22] and *Salmonella typhimurium*.[23] The remainder of the microbe is septate, with each mature segment of the body containing between 0 and 2, but typically 1, intrasegmental body, originally thought to be spores.

Presumed Life Cycle and Transmission

There are 2 morphologically distinct types of intrasegmental bodies that are either developing holdfasts or spores, suggesting

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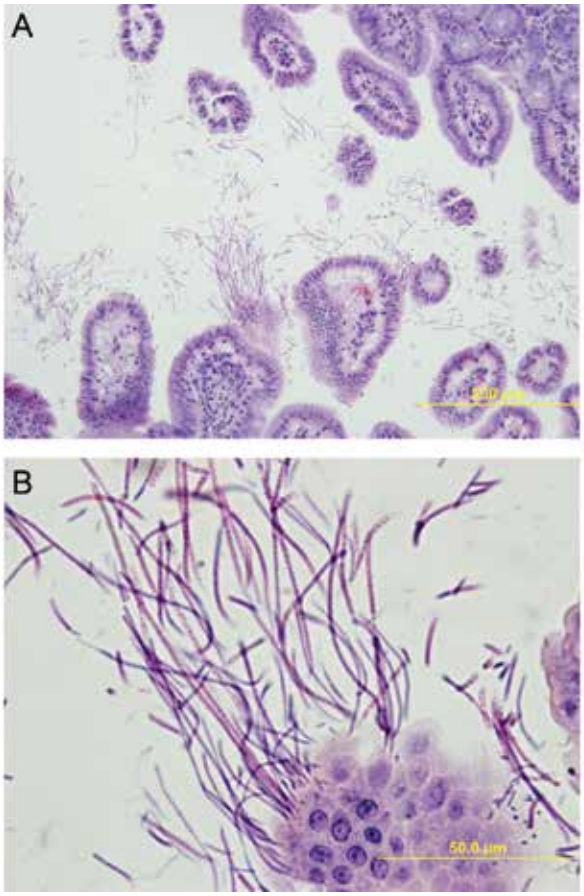

Figure 1. Photomicrographs of a section of segmented filamentous bacteria (SFB) in the ileum of a weanling (age, approximately 3 to 4 wk) female C57BL/6 mouse. Hematoxylin and eosing stain; magnification, 200× (A), 1000× (B).

that SFB exist in both vegetative and dormant forms.[10] Both types of intrasegmental body appear to increase during maturity in the proximal to distal direction, and functional holdfasts or spores are thought to be released from the mature distal segments of the microbe. However, much of the knowledge of the life cycle of SFB has been deduced from microscopy and, because all attempts to culture the organism have been fruitless,[14,46] there are still many uncertainties regarding these microbes. For example, one can infer that SFB must complete a full life-cycle within 2 to 3 d, given the rapid turnover of intestinal epithelial cells in rodents. Similarly, because SFB are considered obligate anaerobes and because spores are seen free in the lumen of infected rodents,[69] SFB presumably spread via inoculation with spores. Although several factors, including diet and the immune status of both the dam and pup, affect colonization by SFB,[43,47,52] once the organisms are introduced into a colony, they are transmitted vertically and have the potential to become endemic.[13] Longitudinal studies of the developing ileum have confirmed that SFB appear in juvenile mice at around 20 d of age and that, during the earliest stage of colonization, the SFB themselves are transiently colonized by other rod-shaped bacteria.[51] Soon thereafter, SFB proliferate to the point that they are one of the dominant bacterial genera present in the gut (Figure 3) before receding to the levels seen in adults.[78] Given these features, the first few weeks after weaning may represent the optimal testing window for the determination

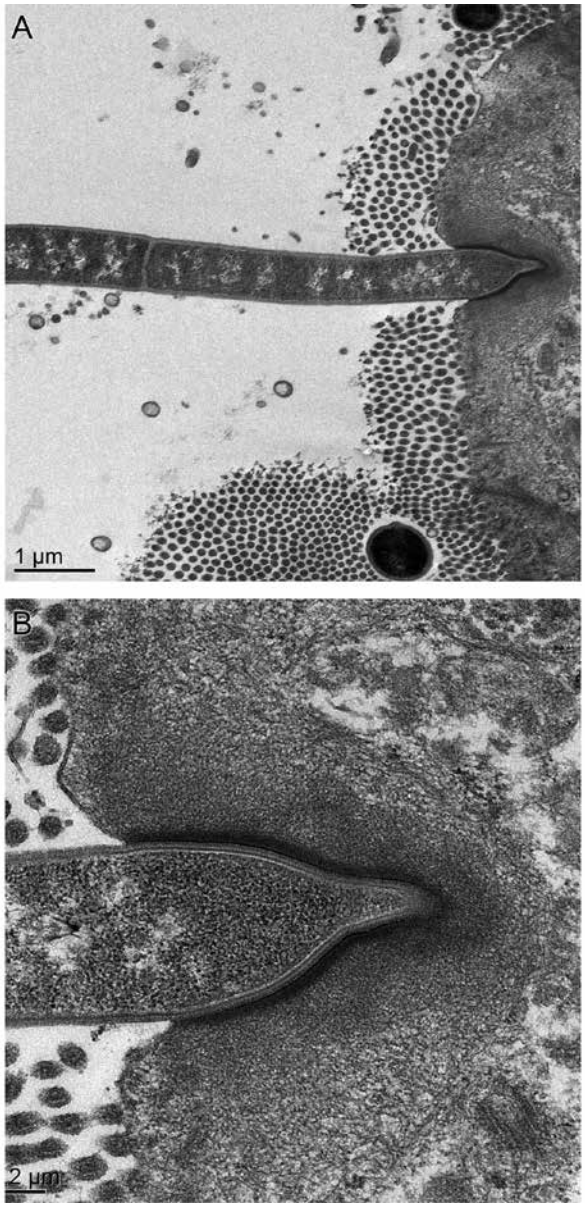

Figure 2. Transmission-electron–microscopic images demonstrate the holdfast of a segmented filamentous bacterium (SFB) attached to the ileal epithelium of a weanling (age, approximately 3 to 4 wk) female C57BL/6 mouse. Magnification: 27,000× (A); 90,000× (B).

of SFB status in a mouse colony. Current diagnostic modalities include histologic examination of the ileum and PCR-based methods. Histologic examination requires an experienced pathologist to differentiate SFB from the myriad smaller filamentous microbes in the gastrointestinal tract and is a postmortem assay. Alternatively, multiple primer sets designed against the 16S rRNA gene have been published,[24,77] allowing for noninvasive screening of feces from rodents. This evaluation can easily be performed in-house, and these services are commercially available for rats and mice.

Host Specificity

There is now evidence that SFB-like bacteria exist in a broad range of species, including rhesus macaques (*Macaca mulatta*),[48]

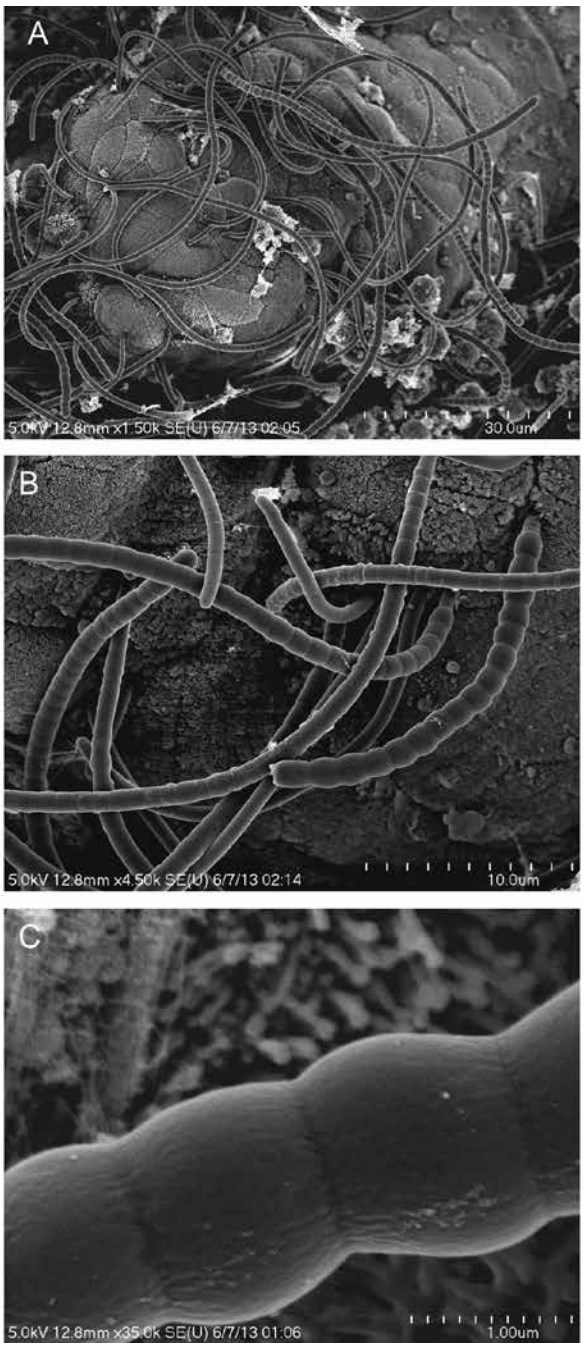

Figure 3. Scanning-electron–microscopic images of segmented filamentous bacteria (SFB) in the ileum of a weanling (age, approximately 3 to 4 wk) female C57BL/6 mouse. Magnification: 1500× (A); 4500× (B); 35,000× (C).

crab-eating macaques (*M. fascicularis*),[48] vervet monkeys (*Cercopithecine aethiops*),[6] African gorillas (*Gorilla* spp.),[67] South African claw-footed toads (*Xenopus laevis*),[48] carp (*Cyprinus carpio*),[48] rainbow trout (*Oncorhynchus mykiss*),[17,92] wood mice (*Apodemus sylvaticus*),[48] guinea pigs (*Cavia porcellus*),[46] rabbits (*Oryctolagus cuniculus*),[33] horses (*Equus caballus*),[58] cattle (*Bos taurus*),[75] pigs (*Sus scrofa domestica*),[70] cats (*Felis catus*),[48] turkeys (*Meleagris gallopavo*),[5,68] jackdaws (*Corvus monedula*),[48] and magpies (*Pica pica*).[48] Perhaps not surprisingly, SFB have been reported to occur in humans as well, although there are conflicting data regarding the persistence of colonization of adults. In the first published report of SFB in humans, SFB were visualized via light microscopy and were adherent to biopsied tissue from 1 of the 6 adults examined.[48] Conversely, a recent attempt to confirm the presence of SFB in humans by searching for any part of the SFB genome in 263 human metagenomic data sets was unsuccessful. Similarly, attempts to detect SFB by using PCR designed to amplify 5 different SFB-specific genes from 8 freshly evacuated human fecal samples were fruitless also.[73] These divergent findings may be rectified by a recent study wherein SFB were found to colonize humans in an age-dependent manner. SFB were detected by PCR in 25% (2 of 8) of infants younger than 6 mo of age and in 78.6% (11 of 14) of infants 7 to 12 mo of age.[95] However, the same study reported a prevalence of only 6.2% (10 of 162) in subjects between the ages of 3 and 75 y. Therefore, it appears that SFB commonly colonize the gut of humans early in life but then are cleared in most persons by 3 y of age. An age-dependent decrease in SFB colonization may occur in other species (for example, dogs, chickens, horses, and pigs) as well.[33,58] Also of interest is a recent retrospective histologic survey of the ileocecal valves of patients diagnosed with ulcerative colitis or Crohn disease (the 2 primary forms of inflammatory bowel disease) and patients without a history of intestinal inflammation.[8] Whereas 100% (6 of 6) patients with ulcerative colitis were colonized by high levels of SFB, the organism was found in none (0 of 6) of the patients with Crohn disease and was present only at low levels in 50% (3 of 6) of the control samples. Clearly the relationship between SFB and inflammatory bowel disease or other conditions in humans merits further investigation.

SFB selectively colonize the ilea of all species examined (with the exception of rainbow trout and carp, which lack well-differentiated ilea, and chickens, in which SFB also colonize the cecal tonsils[28]). Because SFB are highly dependent on other organisms for nutrients, it is tempting to speculate that the microbes colonize the gut in such a site-specific manner due to a relatively greater availability of a particular host-derived factor, such as cobalamin (vitamin B12), in that region. Alternatively, the ileum is also the region of the gut wherein bacterial densities increase dramatically, potentially providing some essential microbially produced factor. There are also species-specific differences in the predominant site of SFB attachment within the ileum. In pigs and most rodents, SFB adhere to both absorptive villi and the follicle-associated epithelium overlying Peyer patches; in mice and horses, however, there is a reported preference for attachment to the follicle-associated epithelium.[7,40,46,58] Alternatively, microscopic examination of ilea from dogs,[35] cows,[75] and rabbits[33] revealed SFB attached primarily to the absorptive villi. At the cellular level, SFB appear to be capable of binding to the apical surface of classic absorptive enterocytes, specialized M cells, and goblet cells, as well as to the tight junctions between these cells.[7,40,63] In addition, another study documented SFB in direct contact with intraepithelial mononuclear cells.[63] The portion of the filament in contact with the host cell appeared to be degenerating, leading to the speculation that the microbe was in an early stage of phagocytosis, a process that has been noted elsewhere.[94]

The first piece of evidence that SFB exhibit host specificity came from experiments wherein germ-free rats and mice were gavaged with ileal homogenates from both species, in which SFB could subsequently be found in only those animals that had received the

ileal microbiota derived from its cognate host species.[84] Studies performed with mice and chickens reached a similar conclusion,[1] yet the phylogenetic relation of these host-specific SFB to each other and to other microbes remained unclear. A breakthrough in the study of SFB occurred with the successful monoassociation of germ-free mice via intraileal inoculation with ethanol-treated ileal contents of donor mice.[49] In the absence of an effective method of culture, this protocol yielded a pure sample for sequencing of the 16S rRNA gene in mouse SFB.[76] Comparison of the 16S rRNA sequence of mouse SFB with metagenomic data from rats, chickens, and macaques revealed that the microbes belong to a distinct group within the phylum *Firmicutes*, putatively serving as a novel genus in the order *Clostridiales*.[36,76,77] Sequencing of the complete genomes of rat and mouse SFB has confirmed that they are indeed closely related to—but distinct from—recognized *Clostridium* spp.[67] In addition, comparison of 16S rRNA sequences of SFB isolated from mice and rats with existing sequences generated from fecal samples of multiple diverse species including gorilla,[57] macaque,[36] dog,[81] and rainbow trout[92] demonstrated 94% to 98% nucleotide identity, forming a distinct cluster separate from other *Clostridium* spp. (Figure 4). It should be noted that although SFB have also been reported to occur in numerous invertebrate species, including myriapods, termites, cockroaches, isopods, and beetles,[46,56] 16S rRNA analysis has placed those microbes in the family *Lachnospiraceae*, rather than *Clostridiaceae*, and thus distinct from the SFB found in vertebrate species.[85,86] Similarly, reports of long segmented filamentous organisms associated with visceral granulomatous disease,[34] stunting syndrome,[2] diarrhea, and increased mortality[29] in chickens, turkeys, and quail must be evaluated cautiously. Considering the presence of these long segmented filamentous organisms in the jejunum,[2,29] their occasional branching morphology,[2] and their association with overt disease, it is more likely that these are microbes distinct from SFB, such as perhaps *Actinomycetes* spp. or *Nocardia* spp. The fact that microbes more akin to the SFB characterized in rodents have been identified in the cecum of healthy turkey poults[5,68] makes this interpretation even more likely. Regardless, molecular techniques will need to be used to answer this question definitively.

Genome and Molecular Biology

Considering the mutualism implied by the close association of SFB with the ileal enterocytes and lack of inflammation, Davis and Savage posited that SFB coevolved with mice and rats and that the microbe may rely on the host for nutrients.[13] Providing strong support for that insight, 3 groups have now independently sequenced the complete genome of mouse SFB[54,67,73] with one of them also sequencing the genome of rat SFB. In addition, a fourth group has performed single-cell sequencing of 5 individual SFB filaments.[65] The genome of mouse SFB encodes a single circular chromosome of between 1.57 and 1.62 Mb with a G+C content of approximately 28%, similar to that found in other obligate symbionts. SFB possess a remarkably reduced genome relative to closely related *Clostridium* spp. and lack genes responsible for the synthesis of the majority of amino acids, nucleotides, vitamins, and cofactors. Conversely, several transporter and permease genes, necessary for the uptake of extracellular nutrients, are found in the genomes of both rat and mouse SFB. In addition, SFB likely facilitate the acquisition of nutrients through the degradation of host and dietary proteins; the rat SFB genome contains putative genes for 28 proteases and 53 peptidases, several of which probably are secreted.[67] Expectedly, there are also many genes involved in sporulation and germination homologous to those found in clostridial species, although the triggers for these processes are unknown. Although exposure to oxygen is presumably one cause for sporulation, the fact that spores are constitutively released in the ileum[69,75] suggests that sporulation may be an ongoing process in the life cycle of SFB. In addition, the presence of genes encoding peroxidase and catalase proteins implies that SFB may be able to survive in microaerophilic environments.

The presence of multiple coding DNA sequences of bacteriophage origin in the genomes of both rat and mouse SFB imply that SFB are subject to foreign invading DNA. Some of these coding DNA sequences are highly similar to those found in *Clostridium* spp., suggesting horizontal gene transfer may have occurred. In addition, the genomes of both mouse and rat SFB contain clustered, regularly interspaced, and short palindromic repeat (CRISPR) loci, which function as acquired components of prokaryotic immune systems. These loci are found in a large percentage of sequenced bacteria and archaea and are thought to serve as an indicator of past exposure to invading DNA.[3,60]

One of the most fascinating findings in the genomes of rat and mouse SFB is the presence of genes encoding multiple flagellar assembly proteins, including 4 different flagellin loci in rat SFB and 3[67] or 4[54] in mouse SFB. Although no evidence of SFB motility has ever been documented, the presence of a complete set of chemotaxis genes and an absence of recognizable pseudogenes in the flagellin gene sets suggest that SFB may possess chemotactically driven flagellar motility.[54] That being said, rat SFB also possess genes encoding several type IV pilus proteins,[67] previously shown to be involved in a twitching motility.[61] In addition, flagellar assembly proteins can be applied to uses other than motility, such as type 3 secretion systems or as adhesins.[73] Therefore, the exact method of motility used by SFB remains a mystery, although the presence of multiple genes involved in chemotaxis, along with the organism's ability to penetrate the mucus layer lining the intestinal epithelium, suggest that SFB are at least transiently motile.

Effects on Host Physiology

SFB historically have been considered members of the commensal microbiota. However, it is now becoming very clear that their presence can have a profound influence on models of intestinal disease as well as systemic immune-mediated diseases. How often has the laboratory animal veterinarian heard the comment "My model worked fine at my old institution"? Could such anecdotes of altered model phenotypes be associated with subtle changes in commensal microbiota, such as the addition of SFB? The following paragraphs highlight the current knowledge regarding the influence of SFB on the development and homeostasis of several components of the mucosal immune system. Given that our understanding of SFB is still in its infancy, the reader is encouraged to regularly review the literature for new information that is likely to emerge about these bacteria, as well as other members of the commensal microbiota.

Interest in a functional role of SFB in host health was initially spurred by evidence suggesting that SFB contributed to colonization resistance to the enteric pathogen *Salmonella enteritidis*.[27] One group showed that in rats experimentally infected with a virulent strain of *S. enteritidis*, the presence of SFB and *Salmonella* on the ileal epithelium of individual villi is mutually exclusive, implying

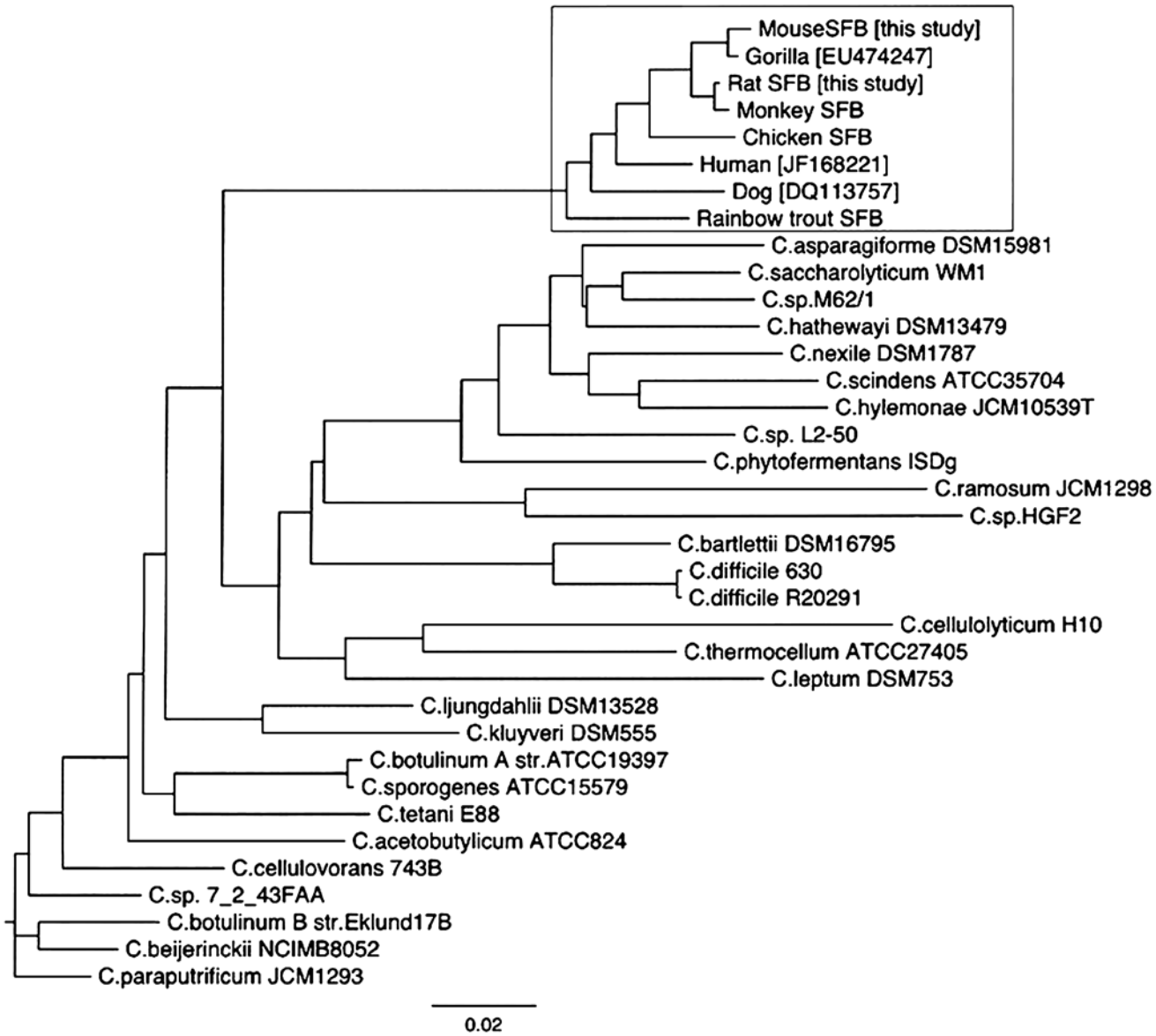

Figure 4. Phylogenetic tree based on 16S rRNA sequences of segmented filamentous bacteria (SFB); the 16S sequences from mouse and rat SFB and 3 additional sequences identified in reference 67; 3 published sequences from chicken, rainbow trout, and monkey SFB; and 28 *Clostridium* strains. A distinct clade composed of 16S sequences derived from 8 hosts, including mouse and rat, is boxed. Reprinted from reference 67 with permission of the publisher.

that SFB not only physically compete with pathogenic microbes for binding spots on enterocytes but that they also induce a local response that hinders the ability of *S. enteritidis* to adhere to the epithelium. Similarly, the presence of SFB on the ileal villi of rabbits correlates with resistance to enteropathogenic *Escherichia coli*, another microbe known to enter the host through ileal Peyer patches.[33] Using mice in which the microbiota differed by only the presence or absence of SFB, one group showed that SFB increases resistance to colonization by another microbe of the family *Enterobacteriaceae*, *Citrobacter rodentium*.[37] Notably, the influence of SFB on colonization resistance likely requires the presence of other commensal microbes, because SFB-monoassociated mice fare no better than do germ-free mice when challenged with *S. enterica* serovar Typhimurium.[11]

Effects on the Host Immune System

With the possible exception of rainbow trout,[15-18] no host has ever been documented to show an inflammatory response, either grossly or microscopically, to naturally occurring colonization with SFB. That being said, SFB are clearly not idle bystanders in their interactions with the complex mucosal immune system. Compared with germ-free mice, mice monoassociated with SFB have significantly higher numbers of intestinal IgA-secreting cells and significantly higher IgA titers in the intestines and serum. Remarkably, monoassociation of germ-free mice with SFB restores the production of IgA to levels close to those seen in SFB-negative SPF mice.[50,91] One group extended these findings to show that SFB induce not only specific IgA production but also 'natural' nonspecific IgA production, with SFB-specific IgA production

comprising less than 1.4% of total IgA.[83] Conversely, maternal IgA production has been shown to inhibit SFB colonization of pups during suckling,[43] perhaps explaining early reports from conventionally housed mice that SFB is not evident in pups until just before weaning.[71] SFB undergo robust proliferation after weaning but then decline to a basal level shortly thereafter, presumably due to host-derived IgA.[9,64] The presence of IgA apparently impedes the proliferation of SFB in adults also, because mice lacking activation-induced cytidine deaminase, an enzyme critical in hypermutation of IgA, experience a selective overgrowth of SFB despite the presence of other commensal organisms.[82]

In addition, SFB influence the development of the T-cell repertoire. SFB enhance the development of activated $CD45RB^{low}$ $CD4^+$ T-helper cells in Peyer patches[83] and the expansion of both ααTCR-[11] and αβ TCR-bearing intraepithelial lymphocytes.[90,91] In stark contrast to experiments performed with mice monoassociated with various members of the dominant bacterial phyla in the gut (including *Bacteroides thetaiotaomicron*, *B. vulgatus* [phylum *Bacteroidetes*], 3 different *Clostridium* spp. from the Altered Schaedler Flora [phylum *Firmicutes*], and *E. coli* [phylum *Proteobacteria*]), monoassociation with SFB recapitulates many of the immunologic effects of a complex microbiota.[26] To this end, SFB induce a full retinue of homeostatic $CD4^+$ T-helper–cell profiles including T_H1, T_H2, T_H17, and T_{reg} cells, with the most pronounced effect being on the T_H17 type. The T_H17 response induced by SFB is linked to the induction of antimicrobial responses and increased colonization resistance to pathogenic *Enterobacteriaceae*.[37] This outcome is likely due to the protective effects of IL22, a canonical T_H17 cytokine known to induce the production of antimicrobial peptides efficacious against bacteria capable of inducing attaching and effacing lesions such as *C. rodentium* and certain strains of *E. coli*.[96]

The presence of flagellar proteins may explain the ability of SFB to induce IgA production as well as T_H17 immune responses. One laboratory showed that recombinant gene fusion proteins of 3 of the 4 mouse SFB flagellins activated the NFκB signaling pathway in a Toll-like receptor (TLR) 5-dependent manner.[54] TLR5 is a pattern recognition receptor of the innate immune system expressed primarily on the $CD11c^{hi}CD11b^{hi}$ subset of intestinal dendritic cells, and binding of flagellin has been shown to induce class-switching to IgA and the differentiation of T_H17 cells.[88,89] Of note, this subset of dendritic cells was demonstrated to be solely responsible for the differentially greater production of IL17 in the gut of C57BL/6 mice harboring SFB (from Charles River Laboratories) relative to C57BL/6 mice lacking SFB (from The Jackson Laboratory).[19] The binding sites of flagellin and TLR5 have been identified[39] and, notably, the specific motif capable of binding TLR5 is highly conserved in the flagellar proteins of SFB, whereas this motif is absent in all commensal *Clostridium* spp. examined except *C. sporogenes*.[67] Therefore, it seems plausible that SFB invoke the production of IgA and the differentiation and proliferation of T_H17 cells through the sensing of SFB-specific flagellin proteins by TLR5 expressed by the $CD11c^{hi}CD11b^{hi}$ subset of intestinal dendritic cells.

In addition to adaptive immunity, colonization with SFB influences the innate immune system. Colonization of germ-free mice with SFB—but not a mixture of *Clostridium* spp.—leads to increased expression of MHC class II molecules on intestinal epithelial cells.[90,91] SFB also influence the glycosylation of enterocytes, specifically inducing the expression of fucosyl asialo GM1 glycolipids, posited to inhibit the attachment of other adherent microbes.[30,90] In addition, SFB have been found to contribute to innate immunity via enhanced production of IFNγ by NK cells and the induction of RegIIIβ and RegIIIγ on intestinal epithelium,[45] a result that was duplicated by a different research group.[37]

Effects on Animal Models

As our understanding of the role of SFB in the maturation of the immune system has grown, several researchers have applied SFB as an experimental variable to assess its effect on inflammatory disease models. In one commonly used model of inflammatory bowel disease, $CD4^+CD45RB^{high}$ effector subsets of T cells isolated from the spleen of conventional mice are adoptively transferred to SCID mice to induce severe colitis whereas cotransfer of $CD4^+CD45RB^{low}$ cells prevents the development of inflammation.[66] As in most models of inflammatory bowel disease, the development of inflammation in the described model is dependent on the presence of intestinal microbiota. Efforts to determine the minimal bacterial community needed to allow for inflammation demonstrated that SCID mice monoassociated with SFB do not develop colitis after transfer of $CD4^+CD45RB^{high}$ T cells,[44] whereas SCID mice colonized with a very limited defined (SPF) microbiota develop mild to moderate inflammation by 12 wk after transfer.[80] Interestingly, the addition of SFB to the SPF microbiota consistently results in severe colitis in recipient mice, suggesting that SFB exert a synergistic effect with other commensal bacteria in providing an environment conducive to intestinal inflammation.[80]

Collectively, the above findings highlight the importance of SFB in the development and modulation of several components of the mucosal immune system including innate, humoral, and cell-mediated components. Given the importance of mucosal immunity to virtually all models of intestinal disease, the fact that SFB has such profound influence on this system raises many questions regarding its effect on models of intestinal disease. Moreover, there is growing evidence that the mucosal immune system has key interactions with the development and homeostasis of systemic immunity. Therefore the breadth of models potentially altered by the presence or absence of SFB is expanded greatly. For example, other groups have now shown that SFB exacerbates inflammation in models of extraintestinal disease as well, including experimental autoimmune encephalomyelitis[55] and autoimmune arthritis,[93] in a T_H17-dependent manner. Interestingly, SFB appear to confer protection from diabetes in nonobese diabetic mice, and in a sex-dependent manner,[53] raising another potentially crucial set of questions regarding differential effects of SFB, and perhaps other microbes, on male and female subjects.

Implications Regarding Other Commensal Microbes

The growing evidence that SFB can modulate mucosal health and subsequently alter rodent model phenotypes raises the question "What about other members of the microbiota?" Clearly, SFB are not the first autochthonous bacteria to be identified as having an effect on disease models. *Helicobacter* spp., still prevalent in many research colonies but often unreported in the literature, can be considered commensal microbes in some strains of mice but also may be necessary components for the phenotypes of various disease models.[59] As with SFB, *Helicobacter* spp. may influence host physiology, such as by affecting immune responses to

other commensal bacteria present in the gut.[41,42] Similarly, several conceptual models have been proposed wherein key microbes modulate the composition of the microbiota thereby increasing its overall inflammatory potential.[31,74,87] Therefore, the widespread influence of various microbes on other members of the microbiota as well as the host, coupled with the fact that the majority of the intestinal microbiota is resistant to culture in vitro, make it highly likely that other gut microbes with unappreciated effects on disease models will be identified in the future. In addition, studies of the human microbiota in persons with various diseases often find correlations between disease and shifts in the relative abundance of higher taxa, such as differences in the ratio of *Firmicutes* to *Bacteroidetes*. Although many of these findings are correlative, they beg the question, "Is there a core microbiota in rodents that is necessary for normal mucosal immunity?" If so, what are the functions of that microbiota and the effect of subtle alterations in its composition? We have already begun a paradigm shift in our analyses of the microbiota, through next-generation sequencing technologies and bioinformatics-based approaches. These and other interdisciplinary methods will be needed for inclusive and robust assessments of the microbiota and the identification of other commensal microbes that affect animal models of disease.

Conclusions

Although the existence of SFB has been recognized for several decades, these organisms have entered the forefront of microbial and metagenomic research only in the last several years. Having carried multiple erstwhile names (bacillus of Savage, *Candidatus* Arthromitus, and now *Candidatus* Savagella[62]), SFB have rightly attracted attention due to their role as a 'type species' with the capacity to induce the development of multiple adaptive immune responses in the gut. For microbiologists and immunologists, SFB provide a unique model organism for investigation of the development of the immune system and host–microbe interactions. For all scientists using mice or rats in their research, SFB must be considered as a potential variable with a potential impact on outcomes. Similarly, SFB is but one organism within a complex and dynamic mixture of microbes, and the entire commensal microbiota needs to be considered when model phenotypes are altered or completely lost, particularly when changes in diet or environment are present. It must be remembered that only a minority of intestinal bacteria are amenable to culture,[20] and everything known about SFB stems from those first observations of a bacteria with unique morphology and size. Doubtless, molecular metagenomic approaches eventually will identify other microbes with profound effects on host immunology and physiology, offering new insights into human and animal health.

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