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The human symbiont *Mucispirillum schaedleri* − causality in health and disease

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Abstract

Trillions of bacteria inhabit the mammalian gastrointestinal tract. In the majority of hosts, these symbionts contribute largely to beneficial functions promoting microbe-host homeostasis. However, an increasing number of human diseases is associated with altered microbiota composition and enrichment of certain bacterial species. A well-known example of this is *Mucispirillum schaedleri*, which has been associated with inflammatory conditions in the intestine. *Mucispirillum* spp. belong to the phylum Deferribacteres and are prevalent but low abundant members of the rodent, pig and human microbiota. Recently, *Mucispirillum schaedleri* was causally linked to the development of Crohn's disease − like colitis in immunodeficient mice. While this study certifies a considerable pathogenic potential, the same organism can also promote health in the immunocompetent host: *M. schaedleri* protects from *Salmonella enterica* serovar Typhimurium (*S.* Tm)-induced colitis by interfering with the expression of the pathogen´s invasion machinery. In this review, we summarize the current knowledge on the mammalian gut symbiont *M. schaedleri* and its role in intestinal homeostasis and discuss open questions and perspectives for future research.

Keywords

Pathobiont; colitogenic; dysbiosis; microbiome; Crohn´s disease; Ulcerative colitis; inflammation

Ecology of *Mucispirillum schaedleri*

Eubacterial communities in the gut of vertebrates are dominated by the Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. Low abundance phyla include Fusobacteria, Verrucomicrobia, Spirochaetes and Deferribacteres. Deferribacteres [1], comprise two families, Deferribacteraceae and Calditrichaceae, that mostly group environmental genera (e.g. *Calditerrivibrio*, *Deferribacter*, *Denitrovibrio*, *Flexistipes*, *Geovibrio, Seleniivibrio and Petrothermobacter*) living in hot springs, deep-sea or sediments [2–8]. *Mucispirillum* is, as of today, the only genus of the Deferribacteraceae known to inhabit the vertebrate gastrointestinal tract [9–12]. The type species, *Mucispirillum schaedleri* HRI I17 was first isolated from intestinal mucus scrapings of laboratory mice [13]. Sequence-based surveys of the mouse gut microbiota have consistently detected this species in mouse intestinal samples. While it shows a low relative abundance in murine feces (˜ 1%), it is enriched in the colonic mucus (relative abundance up to 10%) [14–16]. To gain more insights in the ecology of *M. schaedleri*, we determined the prevalence of

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this organism in host-associated and environmental samples by conducting a 16S rRNA gene amplicon-based survey in published datasets contained in IMNGS [17]. Our results are in line with previous reports on the occurrence of *M. schaedleri* in the intestinal tract of various animals. Compared to environmental samples, a higher prevalence of *M. schaedleri* was found in host-associated samples, in particular derived from the gut of rodents and pigs (Fig. 1A). Highly similar sequences (>99% identity) were also detected in the gut of cattle, fish and humans, but at lower prevalence. Strikingly, *M. schaedleri* was detectable in a significant fraction of human nasal samples, at low relative abundance (Fig. 1B). Other environmental samples harbored sequences at 97% identity and below. Interestingly, a fraction of soil and insect gut samples also harbored *M. schaedleri* sequences.

Relative abundance of *M. schaedleri* was only determined for host-associated samples (Fig. 1B). The highest relative abundance was clearly found in mouse-derived specimen, followed by samples from pig, chicken, rat and human gut. The mean relative abundance of *M. schaedleri* in the human gut was clearly below 0,1%. It was previously shown that the prevalence of *M. schaedleri* in human stool samples of healthy individuals is low (detected in 10/339 samples). However, mucosal biopsies exhibited a higher prevalence (e.g. detected in 20/27 jejunum, 12/21 cecum and 11/22 ascending colon) in the same study [16, 18]. Likewise, the mean relative abundance of *M. schaedleri* in human stool samples was 0,02%, while it increased up to 1% in mucosal biopsies. A generally applied procedure in 16S rRNA amplicon sequencing studies is to exclude spurious taxa (<0,25% rel. abundance) [19]. This may explain, why *M. schaedleri* has long been considered to be absent in the human microbiota [20]. Instead, similar to its location in the murine gastrointestinal tract, the bacterium preferentially colonizes the mucus layer and its relative abundance in stool is rather low [10, 16, 18].

Lifestyle and metabolism

M. schaedleri is a spiral shaped, flagellated, Gram^{-} and obligate anaerobic bacterium [13]. It colonizes the intestinal mucus layer but only harbours a very limited set of genes encoding glycan-degrading enzymes [21]. Instead, *M. schaedleri* seems to utilize monosaccharides, amino acids or short-chain fatty acids for energy metabolism [21, 22]. *M. schaedleri* is also enriched at mucosal sites in Anterior gradient 2 protein (Agr2$^{-/-}$)-deficient mice, which have a poorly developed inner colonic mucus layer [16]. This suggests that mucus is not an important prerequisite for *M. schaedleri* colonization. The close proximity of the epithelium represents a rather hostile environment where microbes are exposed to reactive oxygen and nitrogen species [23]. *M. schaedleri* encodes superoxide reductase, catalase, and cytochrome c oxidase genes, which may be important to overcome host defences and colonize mucosal sites [21]. Furthermore, *M. schaedleri* can perform dissimilatory nitrate reduction to ammonia (DNRA) and addition of nitrate enhances its growth *in vitro* [21].

Intestinal inflammation and *M. schaedleri*

A large number of studies have linked *Mucispirillum* spp. to inflammatory bowel disease (IBD) and a variety of other diseases. The result of our (non-exhaustive) literature search is summarized in Table 1. Several studies in mice reported that *Mucispirillum* spp. is

enriched in intestinal samples under conditions of gut inflammation, including genetic and chemical colitis models and infection (Table 1). Moreover, increase of *Mucispirillum* spp. has been linked to high-fat diet, drug treatment, stress and diseases like Rheumatoid Arthritis or Parkinson´s Disease (Table 1). The fact that *M. schaedleri* can respire nitrate, which becomes abundant during inflammatory conditions, may explain blooming of this bacterium in an inflamed environment, as is the case for Enterobacteriaceae [24]. However, so far there is little evidence that *M. schaedleri* can drive disease in an immunocompetent host background. Of note, *M. schaedleri* ASF457 is part of the Altered Schaedler Flora (ASF), a low complex consortium of eight different bacterial species [25] widely used in research on microbiota-host interactions [26]. The ASF is considered as “pathobiont-free microbiota”, which, on its own, does not trigger inflammation. This applies to WT mice but also to several immunodeficient lines (Rag1$^{-/-}$, Rag2$^{-/-}$, Tlr5-/-) and IBD mouse models (IL10$^{-/-}$) [27–29] suggesting, that *M. schaedleri* is not colitogenic within the context of the ASF.

In contrast, a recent study established that *Mucispirillum schaedleri* is causally involved in Crohn’s disease − like colitis in severely immunodeficient mice [30]. Caruso et *al.* found that doubly deficient Nod2^{-}/− Cybb^{-}/− (but not WT or single deficient) mice develop spontaneous colitis when exposed to a specific microbiota. Induction of inflammation was linked to enrichment of *Mucispirillum* spp. in this colitogenic microbiota. Transfer of *M. schaedleri* ASF457 to Nod2^{-}/− Cybb^{-}/− mice triggered colitis, demonstrating that this bacterium indeed is the disease driver. Accumulation of *Mucispirillum* spp. at mucosal sites in doubly deficient mice suggested that impaired neutrophil recruitment and bacterial killing leads to increased tissue loads of *Mucispirillum* spp., which then triggers inflammation. Notably, maternal *Mucispirillum*-specific IgG and IgA protected mice from development of inflammation until weaning and led to increased survival. Further studies reported that *M. schaedleri* triggers T-cell dependent IgA and IgG responses, suggesting that this organism has the ability of efficient immune priming [31, 32]. Robertson et *al.* even isolated *M. schaedleri* from mouse liver samples, suggesting that the species can translocate from the intestinal tract to the hepatobiliary system [13].

Together, this shows that *M. schaedleri* is a mammalian symbiont with elevated pathogenic potential, which is sufficiently invasive to prime adaptive immune responses in a normal host context. Additionally, in a severely immunocompromised host, the invasive character of *M. schaedleri* can trigger intestinal inflammatory responses.

M. schaedleri interferes with *Salmonella* infection

Increasing evidence exists, that the same bacterial strain termed as “pathobiont” could also exert health-promoting functions on its host in a different scenario [33]. Along these lines, we demonstrated a beneficial role of *M. schaedleri* in the context of non-typhoidal *Salmonella enterica* serovar Typhimurium (*S.* Tm) infection [16]. *Salmonella* is a food-borne pathogen and a major cause of self-limiting gastroenteritis in humans. The intestinal microbiota broadly protects from *S.* Tm by different mechanisms, including competition for substrates, production of antimicrobial compounds and strengthening of barrier functions [34]. When ingested, *Salmonella* has to colonize the gut lumen to high levels in order

to invade the intestinal epithelium and subsequently induce intestinal inflammation [35]. Invasion into epithelial cells is mediated by employing its major pathogenicity factor, a type 3 secretion system encoded on the *Salmonella* Pathogenicity Island-1 (SPI1-T3SS) [36]. We found that Agr2$^{-/-}$ mice which exhibit an impaired mucus layer, were protected from *S.* Tm induced inflammation [16]. This correlated with a vast increase in relative abundance of *M. schaedleri* at mucosal sites in Agr2$^{-/-}$ but not isobiotic Agr2$^{+/-}$ control mice. Experiments using mice associated with defined microbiota revealed that *M. schaedleri* cannot block *S.* Tm colonization but delay the onset of *S.* Tm colitis by several days. The underlying reason is that *S.* Tm downregulated its SPI1-T3SS in the presence of *M. schaedleri*. Since high levels of NO_3^- promote expression of the SPI1-T3SS, it is conceivable that competition for NO_3^- is the underlying mechanism how *M. schaedleri* blocks *S.* Tm virulence. This study provided the first evidence of an intestinal symbiont which can block virulence functions of a major human enteric pathogen.

Concluding remarks

M. schaedleri is a prevalent symbiont of the gut microbiota of humans and various animals. Due to its low relative abundance in human fecal samples, it has not been noted in the majority of human studies. In mouse models *Mucispirillium* spp. have been associated with several disease conditions but *M. schaedleri* can also promote health by interfering with pathogen invasion. For this reason, *M. schaedleri* may have potential for therapeutic application against human *Salmonella* infection. Obviously, it has to be clarified, whether *M. schaedleri* in general or only specific strains are associated with inflammatory, autoimmune and neoplastic diseases. In addition, future work is needed to study the ecology of *Mucispirillium* spp. in the human and animal gut. 16S rRNA gene amplicon-based survey on published datasets revealed that highly similar sequences (>99% identity) are present in gut samples from humans, mice, rats, other mammals and fish (Fig. 1A). Pigs and chicken show a higher prevalence of less similar sequences (>97% identity), suggesting that there is a higher species diversity. Clearly, a culture collection of *Mucispirillium* spp. isolates from humans and animals will be of great value for future research, as comparative genomic and functional studies of isolates will be required to understand the precise roles of these symbionts in their different host species.

Methods

One 16S rRNA gene sequence (GeneID: 2558850189) representative for *Mucispirillum schaedleri* ASF457 genome (NCBI Taxon ID: 1379858) was obtained from the IMG database [37]. In order to identify the prevalence and relative abundance of *Mucispirillum schaedleri* ASF457 in published 16S rRNA amplicon datasets, we used the IMNGS portal [17] (https://www.imngs.org/16S_rRNA/search/). A list of samples was preselected according to their sources (1) host-associated (for host species, unifying general name and scientific name) and the corresponding body site and (2) environmental sources. The *M. schaedleri* ASF457 16S rRNA gene sequence (GeneID: 2558850189) was used for the similarity search against these selected lists of samples for 90%, 95%, 97% and 99% identity and minimum length of 100 bp. The prevalence was determined as fraction of *M. schaedleri*

ASF457 positive samples of all samples from the respective group. The relative abundance was determined for *M. schaedleri* ASF457 positive samples at 97% identity.

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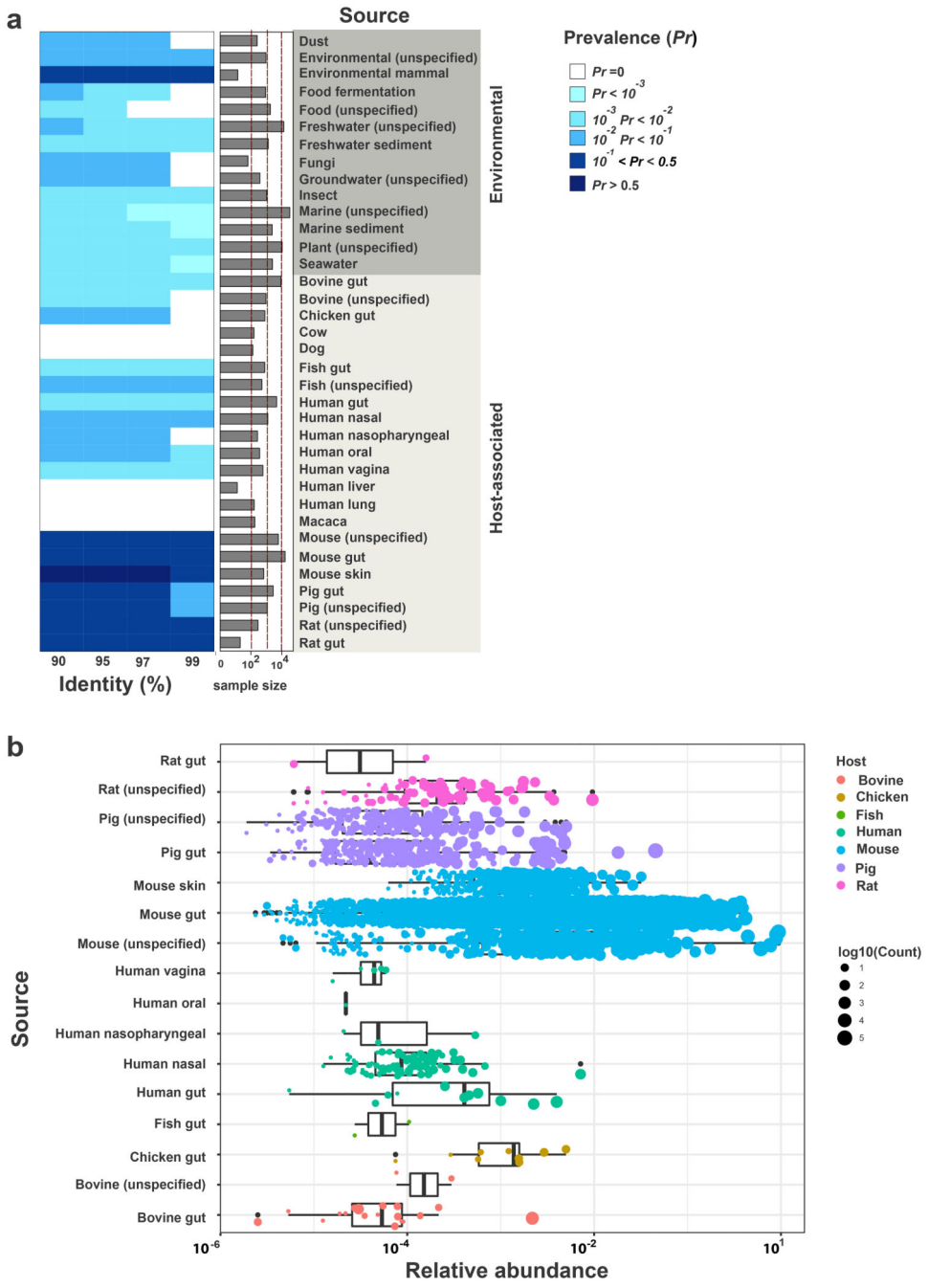

Figure 1. *Mucispirillum* spp. prevalence and abundance in host-associated and environmental microbial communities determined from published 16S rRNA amplicon studies using the IMNGS portal.

(A) Prevalence of *Mucispirillum schaedleri* ASF457 at 90%, 95%, 97% and 99% identity. The y-axis represents the source of the samples, which is organized as “environmental” and “host-associated”. The barplot adjacent to the heatmap represents the sample size from all sources of interest. Prevalence is indicated by different shades of blue. (B) Relative abundance of *M. schaedleri* ASF457 shown for samples with relative abundance > 0 at 97% identity. The x-axis represents log10-transformed relative abundance values and the y-axis

different host-associated sources of interest. The dots within each boxplot represent rel. abundance in individual samples and the size of the dots corresponds to the total number of *M. schaedleri* ASF457 reads detected in the sample at 97% identity.

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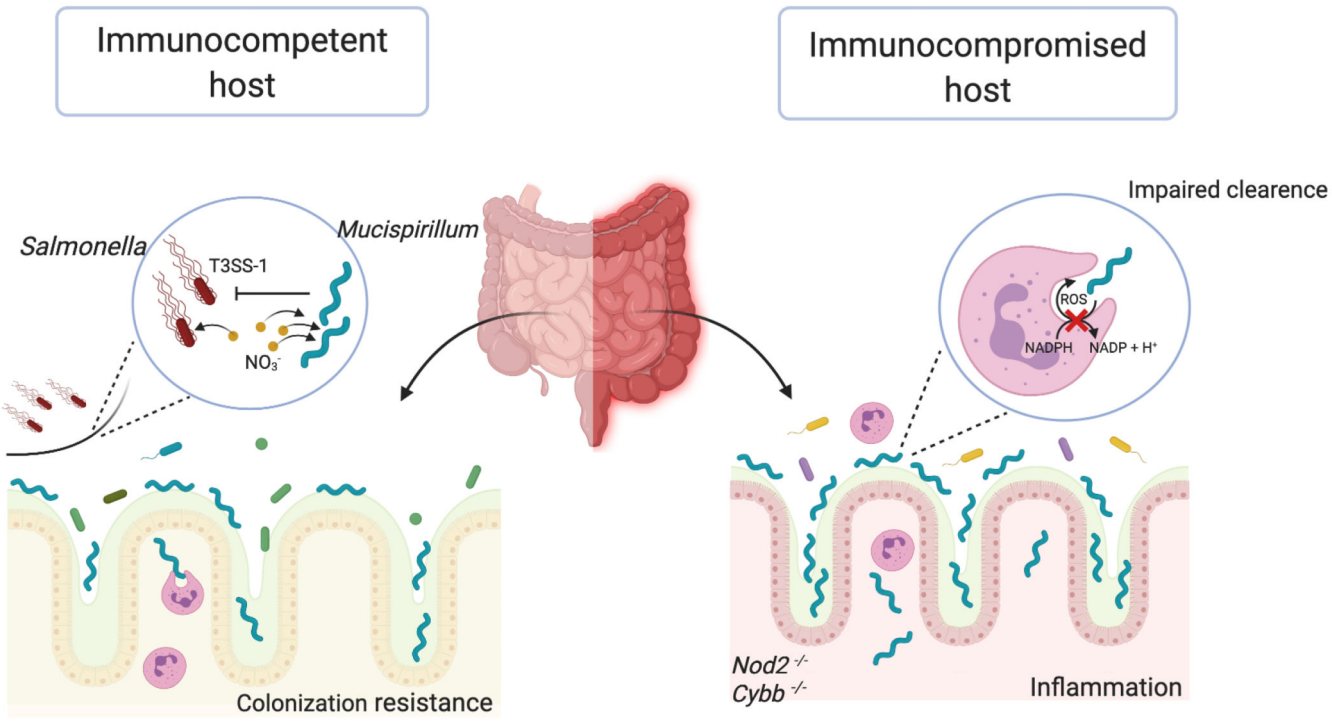

Figure 2. Role of *Mucisprillum schaedleri* in microbiota-host homeostasis.

Mucispirillum schaedleri, is highly prevalent in the murine gut and enriched at the mucosal surface of the colon. In the immunocompetent host (left side), *M. schaedleri* can protect from *Salmonella enterica* serovar Typhimurium (*S.* Tm)-induced colitis by competing for NO_3^- and interfering with the expression of the pathogen´s SPI-1 encoded T3SS. In severely immunodeficient Nod2^{-}/− Cybb^{-}/− hosts (right side), which exhibit deficient neutrophil migration and killing functions, higher numbers of *M. schaedleri* overcome the mucosal barrier and trigger Crohn's disease − like colitis.

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Table 1

Research articles linking *Mucispirillum* spp. to inflammation and disease.

Article	Findings regarding *Mucispirillum* spp.	Associated Disease
[38]	*M. schaedleri is* coated by human derived IgA from patients with Crohn's disease or healthy donors.	IBD
[39]	*Mucispirillum* spp. are increased during active DSS colitis in the murine gut and was identified as indicator species for previous DSS induced colitis.	Dextrane-sulfate sodium (DSS)-colitis mouse model / IBD
[40]	*Mucispirillum* was identified as indicator for DSS-colitis in mice.	DSS-colitis mouse model / IBD
[41]	During early colonization of germ-free mice with a conventional microbiota, *Mucispirillum* spp. are overrepresented which coincides with a proinflammatory milieu.	n.a.
[42]	*Mucispirillum* spp. were enriched during active colitis in TRUC mice (*T-bet*$^{-/-}$*Rag2*$^{-/-}$ ulcerative colitis).	TRUC mice (*T-bet*$^{-/-}$*Rag2*$^{-/-}$ ulcerative colitis)
[43]	*Mucispirillum* spp. were found to be a biomarker for spontaneous colitis in an IBD model (A20$^{IEC/myel-KO}$).	IBD model (A20$^{IEC/myel-KO}$)
[44]	*Mucispirillum* spp. were associated with the pro-inflammatory microbiota of CD1 d$^{-/-}$ mice.	DSS-colitis mouse model; CD1 d$^{-/-}$ *mice*
[31]	*Mucispirillum* spp. induce T-cell dependent IgA in the colon and jejunum.	n.a.
[45]	*Citrobacter rodentium* infection decreases *Mucispirillum* spp. by diminishing its niche during early infection. *Mucispirillum* spp. can only recover during clearance of *C. rodentium.*	Pathogen infection
[46]	Patients with Parkinson's disease exhibit an increased relative abundance of *Mucispirillum* spp.. Those patients also showed higher plasma levels of TNF-α and INF-γ indicating a subinflammatory status.	Parkinson's Disease
[47]	*P. scandens extract reduced inflammatory cell infiltration in a mouse model which was correlated with reduced abundance of Mucispirillum spp..*	Rheumatoid arthritis
[48]	*Mucispirillum* spp. were positively correlated with SLE symptoms in a mouse model. *Mucispirillum* spp. abundance decreased after treatment with a glucocorticoid (prednisone).	Systemic lupus erythematosus (SLE)
[49]	Cholesterol-lowering atorvastatin and rosuvastatin increase the abundance of *Mucispirillum* spp. in high-fat diet fed mice.	Metabolic syndrome
[50]	*Mucispirillum* spp. abundance is increased by stress during pregnancy in mice.	Stress
[51]	*M. schaedleri* was enriched in mice facing social stress.	Social Stress
[52]	*M. schaedleri* was positively correlated with body weight in high-fat diet fed mice.	High-fat diet / metabolic syndrome