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**Abstract**

The intestinal microbiota is the collection of the living microorganisms (bacteria, fungi, protozoa, and viruses) inhabiting the gastrointestinal tract. Novel bacterial identification approaches have revealed that the gastrointestinal microbiota of dogs and cats is, similarly to humans, a highly complex ecosystem. Studies in dogs and cats have demonstrated that acute and chronic gastrointestinal diseases, including inflammatory bowel disease (IBD), are associated with alterations in the small intestinal and fecal microbial communities. Of interest is that these alterations are generally similar to the dysbiosis observed in humans with IBD or animal models of intestinal inflammation, suggesting that microbial responses to inflammatory conditions of the gut are conserved across mammalian host types. Studies have also revealed possible underlying susceptibilities in the innate immune system of dogs and cats with IBD, which further demonstrate the intricate relationship between gut microbiota and host health. Commonly identified microbiome changes in IBD are decreases in bacterial groups within the phyla *Firmicutes* and *Bacte-*

*roidetes*, and increases within *Proteobacteria*. Furthermore, a reduction in the diversity of *Clostridium* clusters XIVa and IV (i.e., *Lachnospiraceae* and *Clostridium coccooides* subgroups) are associated with IBD, suggesting that these bacterial groups may play an important role in maintenance of gastrointestinal health. Future studies are warranted to evaluate the functional changes associated with intestinal dysbiosis in dogs and cats.

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**Key words:** Microbiome; 16S rRNA; Inflammatory bowel disease; Probiotic; Dog; Cat

**Core tip:** Several studies in dogs and cats have demonstrated that acute and chronic gastrointestinal diseases, including inflammatory bowel disease (IBD), are associated with alterations in the small intestinal and fecal microbial communities. Of interest is that these alterations are generally similar to the dysbiosis observed in humans with IBD or animal models of intestinal inflammation, suggesting that microbial responses in inflammatory conditions of the gut are conserved across mammalian host types, and dogs and cats may serve as models to study therapeutic approaches to spontaneous inflammatory conditions of the gastrointestinal tract.

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**INTRODUCTION**

The intestinal microbiota is the collection of the living

microorganisms (bacteria, fungi, protozoa, and viruses) inhabiting the gastrointestinal (GI) tract. Novel bacterial identification approaches have revealed that the gastrointestinal microbiota of dogs and cats is, similarly to humans, a highly complex ecosystem, comprising at least several hundred different bacterial phylotypes<sup>[1-3]</sup>. It has been suggested that the intestine of mammals is home to a total of  $10^{10}$ - $10^{14}$  microbial cells, which is approximately 10 times more than the number of host cells. This complex microbial ecosystem and its interplay with eukaryotic host cells have a significant impact on health and disease of dogs and cats. The stimulation of the host immune system and the microbial metabolites produced by the resident microbiome are thought to be one of the most important driving forces behind the coevolution of gastrointestinal microbiota with their host. Gut microbes aid the host by acting as a defending barrier against enteropathogens. They also aid in digestion of complex fiber sources and produce various short-chain fatty acids and other metabolites that provide nutritional support for enterocytes, and which play an important role in the development and regulation of the host immune system<sup>[4,5]</sup>.

Several studies in dogs and cats have demonstrated that acute and chronic gastrointestinal diseases, including inflammatory bowel disease (IBD), are associated with alterations in small intestinal and fecal microbial communities<sup>[6-14]</sup>. Of interest is that these alterations are generally similar to the dysbiosis observed in humans with IBD or animal models of intestinal inflammation<sup>[15-20]</sup>, suggesting that microbial responses in inflammatory conditions of the gut are conserved across mammalian host types, and dogs and cats may serve as models to study therapeutic approaches to spontaneous inflammatory conditions of the gastrointestinal tract. Recent data support this model, as it has been shown that for example probiotic products (*i.e.*, VSL#3 strains) show similar clinical benefits in dogs with IBD as have been previously demonstrated in humans<sup>[21]</sup>.

Studies have also revealed possible underlying susceptibilities in the innate immune system of dogs and cats with IBD, which further demonstrates the intricate relationship between gut microbiota and host health<sup>[10,22-25]</sup>. Currently, a major hurdle for a more detailed understanding of host-microbe interactions in dogs and cats is the fact that to date most studies evaluating microbiota in GI diseases have examined only a single time point or have evaluated only a small number of diseased animals.

Yet the possibility to alter the microbiome holds promise as a therapeutic mean in veterinary medicine, and recent studies would confirm that direct or indirect manipulations of the intestinal microbiome *via* antibiotics, diet and/or probiotics may have beneficial effects in gastrointestinal diseases of dogs and cats<sup>[21,26-29]</sup>.

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## INTESTINAL MICROBIOTA IN HEALTHY DOGS AND CATS

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Various studies have evaluated the bacterial communities

in healthy dogs and cats using either traditional bacterial culture or novel next-generation sequencing approaches. Based on traditional bacterial culture, the small intestine of dogs and cats harbors generally low bacterial counts, ranging between  $10^2$  to  $10^5$  cfu/g of small intestinal content; however, some studies have identified much higher counts in healthy dogs and cats with up to  $10^9$  cfu/g<sup>[30,31]</sup>. Cats appear to have higher counts of anaerobic bacteria compared to dogs in the proximal small intestine<sup>[31]</sup>. The total bacterial count in the colon ranges between approximately  $10^9$  and  $10^{11}$  cfu/g and the most abundant cultivable groups are *Bacteroides*, *Clostridium*, *Lactobacillus*, *Bifidobacterium*, and *Enterobacteriaceae*<sup>[32,33]</sup>. Next-generation sequencing studies of the 16S rRNA gene have described the canine and feline microbiome, which on higher phylogenetic levels resembles the microbiome of humans and other mammals. On average, 10 different bacterial phyla have been identified in the feline and canine gut, with *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria*, and *Actinobacteria* making up the vast majority of all gut microbes<sup>[1,3,11,34-36]</sup>. Minor abundant members are the phyla *Tenericutes*, *Verrucomicrobia*, *Cyanobacteria*, and *Chloroflexi*. The *Firmicutes* contain various sequences affiliated with *Clostridium* cluster IV and *Clostridium* cluster XIVa and these are together with *Bacteroides* or *Prevotella* the predominant bacterial groups in fecal samples<sup>[3,35,37]</sup>. *Helicobacter* are the predominant group in the stomach (> 90% of sequencing reads)<sup>[38]</sup>, while the duodenum is home to *Enterobacteriaceae*, *Clostridiales*, *Bacteroidales*, and *Lactobacillales*<sup>[36]</sup>.

The canine<sup>[39]</sup> and feline<sup>[40,41]</sup> fecal metagenomes (*i.e.*, shotgun sequencing of genomic DNA) have also been studied. This approach yields information regarding microbial genes present in a sample, and allows assessment of the functional capabilities of the microbiota, summarized in Figure 1. Despite variation in the microbial populations of cats and dogs, the functional capabilities are noted to be highly conserved.

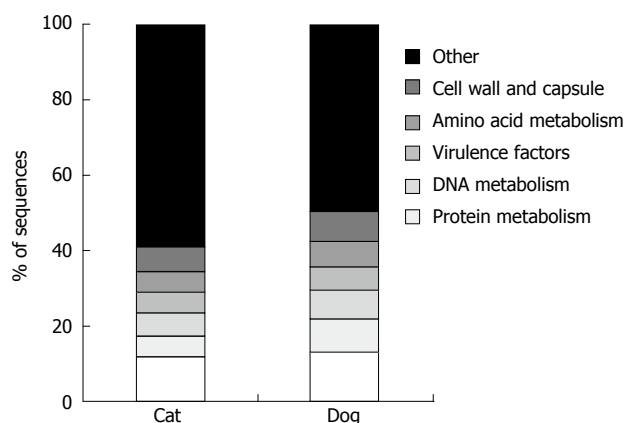
More detailed overviews about the canine and feline microbiota in healthy animals have been reported previously<sup>[42-45]</sup>.

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## MICROBIOME IN GASTROINTESTINAL DISEASES OF DOGS AND CATS

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In recent years, the GI microbiota has garnered strong interest due to the potential etiopathologic role in host health and disease. Many studies in humans and animal models have suggested that various GI disorders are associated with alterations of the GI microbiota. While specific enteropathogens have been recognized in cats and dogs (*i.e.*, *Campylobacter jejuni*, *Clostridium difficile*, *Clostridium perfringens*, and *Salmonella*), most of them are found in similar frequency across healthy animals. Therefore, their cause-effect relations remain unclear<sup>[46,47]</sup>. It is now well recognized that more broad changes in the intestinal microbiome are associated with acute and chronic GI disease. Examples of recent studies in companion ani-



**Figure 1** Relative proportion of major microbial gene functions in cats and dogs. Metagenomic data adapted from Swanson *et al.*<sup>[39]</sup>, Barry *et al.*<sup>[40]</sup>, and Tun *et al.*<sup>[41]</sup>.

mals and their findings are summarized in Table 1. The cause-effect relationships of the alterations are still being elucidated, but especially in chronic enteropathies such as IBD there is now strong evidence that the gut microbiota plays an important part in the pathogenesis of the disease. Studies in humans have shown an association between IBD and microbial dysbiosis in the intestine. In these studies, a decrease in the bacterial phyla *Firmicutes* and *Bacteroidetes*, and an increase in *Proteobacteria* and *Actinobacteria* were associated with IBD<sup>[16]</sup>. Furthermore, a reduction in the diversity of *Clostridium* clusters XIVa and IV (*i.e.*, *Lachnospiraceae* and *C. coccooides* subgroups) are associated with IBD, suggesting that this bacterial group may play an important role in maintenance of gastrointestinal health, possibly due to production of short chain fatty acids (SCFA). Similar studies have now been reported in dogs and cats with IBD, and a comparison of the observed microbial shifts for humans, dogs, and cats with IBD is provided in Table 2.

### Microbiota alterations in canine and feline IBD

In veterinary medicine, chronic enteropathies with intestinal inflammation are commonly seen in dogs and cats. The response to treatment is used to allow for distinction of different types of enteropathies, such as food-responsive diarrhea, antibiotic-responsive diarrhea, and steroid-responsive diarrhea. Idiopathic IBD is a subgroup of enteropathies and it is defined as an inflammation of the GI tract with persistent or recurrent GI signs due to unknown cause<sup>[48]</sup>. To diagnose IBD, known causes for GI inflammation need to be excluded. Therefore, empirical treatments are applied sequentially, starting with a dietary trial, followed by antibiotic therapy if there is a lack of response to diet, and finally, treatment with anti-inflammatory drugs, if response to previous treatments was inadequate. Similarly to human IBD, the exact pathogenesis of canine/feline IBD is unknown, but is suspected to be the result of an abnormal interplay between an altered intestinal microbiota, an underlying genetic susceptibility of the host, and dietary and/or en-

vironmental factors<sup>[48]</sup>. Consequently, several studies have revealed possible underlying susceptibilities in the innate immune system of dogs and cats with chronic GI inflammation. These include altered differential expression of Toll-like receptors (TLR)-2 and 4<sup>[25,49]</sup>, single nucleotide polymorphisms that lead to hyper-responsiveness of TLR-5 to flagellin in German Shepherd dogs (GSDs)<sup>[22]</sup>, and decreased expression of CD11c(+) cells in dogs with IBD<sup>[50]</sup>. There is also well known anecdotal evidence that certain breeds are more prone to chronic GI inflammation. In addition to GSDs, which have been shown to possess polymorphisms in the TLR-4 and TLR-5 genes that are significantly associated with IBD<sup>[51]</sup>, other dog breeds such as Rottweiler, Border Collie, Boxer dog, and Weimaraner have been shown to possess increased risks for developing IBD<sup>[23]</sup>. Of those breeds, breed specific studies evaluating the association between mucosa-adherent microbiota and intestinal inflammation were performed only in GSDs and Boxer dogs. In GSDs with chronic intestinal inflammation, the mucosa-adherent microbiota were analyzed in small intestinal brush samples and showed a significant over-representation of *Bacilli* and *Erysipelotrichi* when compared to healthy Greyhound dogs<sup>[6]</sup>. Interestingly, this is somewhat different to the results observed in other studies where more diverse populations of dogs with chronic intestinal inflammation were evaluated. In these studies, the most frequently observed changes in the mucosa-adherent microbiota in the small intestine were increases in members of the *Proteobacteria*, especially *Escherichia coli*-like organisms<sup>[9]</sup> or *Pseudomonas*<sup>[8]</sup>, with concurrent decreases of members of *Firmicutes* and *Bacteroidetes*. In a more recent study evaluating mucosa-adherent microbiota in the duodenum of dogs with IBD by next-generation sequencing, the proportions of *Fusobacteria*, *Bacteroidaceae*, *Prevotellaceae*, and *Clostridiales* were significantly increased in healthy dogs. In contrast, specific bacterial genera within *Proteobacteria*, including *Diaphrobacter* and *Acinetobacter*, were either more abundant or more frequently identified in dogs with IBD<sup>[7]</sup>. One study evaluated specifically the presence of *Mycobacterium avium* subspecies *paratuberculosis* in duodenal biopsies of dogs with IBD or intestinal neoplasia by qPCR and reported that 19% of diseased dogs were PCR positive for this organism<sup>[52]</sup>. Less published information is available about the mucosa-adherent microbiota of cats with IBD. While sequencing methods have not yet been reported for the characterization of feline IBD, a study using fluorescent *in situ* hybridization (FISH) has revealed an increase in *Enterobacteriaceae* in duodenal biopsies of cats with IBD<sup>[10]</sup>. Furthermore, a relationship between increased bacterial numbers and the severity of histological inflammation was observed<sup>[10]</sup>.

Several studies have evaluated the fecal microbiota in dogs and cats with chronic GI disease. In one study, cats with IBD had lower FISH counts for total bacteria, *Bacteroides* spp., and *Bifidobacterium* spp., but higher counts of *Desulfovibrio* spp. compared to healthy cats<sup>[53]</sup>. *Desulfovibrio* spp. are a sulfate-reducing bacterial group and able to

**Table 1** Reported microbial shifts in dogs and cats with gastrointestinal disease

Ref.	Species	Sampling location	Animal (sample size)	Method	Microbial changes in diseased animals
Suchodolski <i>et al</i> <sup>[1]</sup> , 2012	Dog	Duodenal biopsies	IBD (n = 14) HC (n = 6)	454-pyrosequencing (16S rRNA gene)	Increase in <i>Proteobacteria</i> ( <i>Diaphorobacter</i> , <i>Acinetobacter</i> ) Reduction in <i>Fusobacteria</i> , <i>Bacteroidaceae</i> , <i>Prevotellaceae</i> , <i>Clostridiales</i>
Suchodolski <i>et al</i> <sup>[1]</sup> , 2010	Dog	Duodenal biopsies	IBD (n = 7) HC (n = 7)	Gene clone libraries (16S rRNA gene)	Increase in <i>Proteobacteria</i> Decrease in <i>Clostridia</i>
Allenspach <i>et al</i> <sup>[6]</sup> , 2010	Dog	Duodenal brushings	Chronic enteropathies (n = 13) HC (n = 8)	Gene clone libraries (16S rRNA gene)	Increase in <i>Actinobacteria</i> , <i>Lactobacillales</i> , <i>Erysipelotrichales</i>
Xenoulis <i>et al</i> <sup>[9]</sup> , 2008	Dog	Duodenal brushings	IBD (n = 10) HC (n = 9)	Gene clone libraries (16S rRNA gene)	Increase in <i>Enterobacteriaceae</i> ( <i>E. coli</i> ); Reduction in biodiversity
Suchodolski <i>et al</i> <sup>[36]</sup> , 2008	Dog	Duodenal brushings	Chronic enteropathies (n = 71) HC (n = 64)	Gene clone libraries (fungal ITS gene)	No significant differences in fungal communities
Glanemann <i>et al</i> <sup>[52]</sup> , 2008	Dog	Stomach, duodenum, Colon biopsies	Chronic GI disease (n = 42) HC (n = 14)	PCR	Presence of <i>Mycobacterium avium</i> subspecies <i>paratuberculosis</i> Detected in 8/42 (19%) of dogs with chronic GI disease
Manchester <i>et al</i> <sup>[59]</sup> , 2013	Dog	Colon biopsies	Granulomatous colitis (n = 6)	FISH	Presence of invasive <i>E. coli</i>
Simpson <i>et al</i> <sup>[58]</sup> , 2006	Dog	Colon biopsies	Granulomatous colitis (n = 13) HC (n = 38)	FISH	Intracellular translocation of adherent and invasive <i>E. coli</i>
Rossi <i>et al</i> <sup>[21]</sup> , 2014	Dog	Fecal samples	IBD (n = 20) HC (n = 10)	qPCR (16S rRNA gene)	Decreased in <i>Faecalibacterium</i> spp. And <i>Turicibacter</i> spp.
Foster <i>et al</i> <sup>[62]</sup> , 2013	Dog	Fecal samples	Acute diarrhea (n = 7) HC (n = 12)	454-pyrosequencing (18S rRNA gene)	No significant differences in fungal communities
Suchodolski <i>et al</i> <sup>[14]</sup> , 2012	Dog	Fecal samples	IBD (n = 19) AHD (n = 13) NHD (n = 12) HC (n = 32)	454-pyrosequencing (16S rRNA gene) qPCR (16S rRNA gene)	AHD: most profound alterations in their microbiome Increase in <i>Sutterella</i> , <i>Clostridium perfringens</i> Decrease in <i>Blautia</i> , <i>Ruminococcaceae</i> , <i>Turicibacter</i> IBD: Decrease in <i>Faecalibacterium</i> spp., <i>Fusobacteria</i>
Markel <i>et al</i> <sup>[55]</sup> , 2012	Dog	Fecal samples	Chronic enteropathies (n = 87) AHD (n = 48) HC (n = 180)	qPCR (16S rRNA gene)	Decrease in <i>Faecalibacterium</i> spp., <i>Turicibacter</i> spp., <i>Ruminococcaceae</i> Increase in <i>C. perfringens</i> and <i>E. coli</i>
Jia <i>et al</i> <sup>[65]</sup> , 2010	Dog	Fecal samples	Chronic diarrhea (n = 9) HC (n = 8)	FISH	Increase in <i>Bacteroides</i>
Glanemann <i>et al</i> <sup>[52]</sup> , 2008	Dog	Fecal samples	Diarrhea (n = 4) HC (n = 9)	T-RFLP	Increase in <i>C. perfringens</i> , <i>E. faecalis</i> , and <i>E. faecium</i>
Ghosh <i>et al</i> <sup>[13]</sup> , 2013	Cat	Ileum full-thick biopsies	Severe systemic ill (n = 50) HC (n = 50)	FISH PCR	Increase in <i>E. faecalis</i> Attachment of <i>E. coli</i> to intestinal epithelial cell
Janeczko <i>et al</i> <sup>[10]</sup> , 2008	Cat	Small intestine biopsies	IBD (n = 17) HC (n = 10)	FISH	Increase in <i>Enterobacteriaceae</i>
Abecia <i>et al</i> <sup>[54]</sup> , 2010	Cat	Fecal samples	IBD (n = 8) HC (n = 10)	FISH	No significant differences in specific bacterial population
Inness <i>et al</i> <sup>[53]</sup> , 2007	Cat	Fecal samples	IBD (n = 11) HC (n = 34)	FISH	Decreased total bacteria, <i>Bifidobacterium</i> spp. and <i>Bacteroides</i> Increase in <i>Desulfovibrio</i>

IBD: Inflammatory bowel disease; HC: Healthy control; AHD: Acute hemorrhagic diarrhea; NHD: Non-hemorrhagic diarrhea; FISH: Fluorescence *in situ* hybridization; T-RFLP: Terminal restriction fragment polymorphism; qPCR: Quantitative polymerase chain reaction.

produce hydrogen sulfides, which may be associated with the pathogenesis of feline IBD. However, another study did not identify significant differences in FISH counts

between cats with IBD and controls, although the same bacterial groups were targeted<sup>[54]</sup>. A recent study utilized 454-pyrosequencing of 16S rRNA genes to describe

**Table 2** Comparison of reported microbial shifts in inflammatory bowel disease relative to healthy subjects across species

Organism	Human (Crohn's disease)	Human (ulcerative colitis)	Dog	Cat
Firmicutes	Decreased <sup>115,18,56</sup> 1,2,4,5	Decreased <sup>115,18</sup> 1,2,4	Decreased <sup>17</sup> 1,6	
Class <i>Clostridia</i>			Decreased <sup>17,8,14</sup> 1,2,4,6,7	
Family <i>Ruminococcaceae</i> (Clostridial cluster IV)	Decreased <sup>115</sup> 2,4	Decreased <sup>115</sup> 2,4	Decreased <sup>17,8,14</sup> 1,2,4,6,7	
Family <i>Lachnospiraceae</i> (Clostridial cluster XIVa)	Decreased <sup>115,18</sup> 1,2,4,5	Decreased <sup>115,18</sup> 1,2,4,5	Decreased <sup>17,8</sup> 1,6,7	
Bacteroidetes	Decreased <sup>118</sup> 1,4	Decreased <sup>118</sup> 1,4	Decreased <sup>17,9</sup> 1,6,7; increased <sup>18</sup> 1,7	
Genus <i>Bacteroides</i>			Decreased <sup>17</sup> 1,6	Decreased <sup>153</sup> 1,5
Fusobacteria			Decreased <sup>17,8</sup> 1,6,7	
Proteobacteria	Increased <sup>118</sup> 1,4	Increased <sup>118</sup> 1,4	Increased <sup>17-9</sup> 1,6,7	Increased <sup>110</sup> 1,5
Family <i>Enterobacteriaceae</i>	Unchanged <sup>118</sup> 1,4; increased <sup>20</sup> 2,5	Unchanged <sup>118</sup> 1,4; decreased <sup>20</sup> 2,5	Increased <sup>17-9</sup> 1,6,7	Increased <sup>110</sup> 1,5
<i>E. coli</i>	Unchanged <sup>115</sup> 2,4; Increased <sup>119</sup> 1,4,5		Increased <sup>18</sup> 1,7	
Adherent-Invasive <i>E. coli</i>	Increased <sup>119</sup> 1,5		Increased <sup>158</sup> 1,3,5	
Actinobacteria	Increased <sup>118</sup> 1,4	Increased <sup>118</sup> 1,4	Increased <sup>17</sup> 1,6	
<i>Mycobacterium avium</i> subspecies <i>pseudotuberculosis</i>	Controversial <sup>118</sup> 1		Increased <sup>152</sup> 1,4	
Genus <i>Bifidobacterium</i>	Decreased <sup>115</sup> 2,4	Decreased <sup>115</sup> 2,4		Decreased <sup>153</sup> 1,5

<sup>1</sup>Based on mucosal samples; <sup>2</sup>Based on fecal samples; <sup>3</sup>Granulomatous colitis in Boxer dogs and French bulldogs; <sup>4</sup>Quantitative polymerase chain reaction; <sup>5</sup>Fluorescent *in situ* hybridization; <sup>6</sup>454-Pyrosequencing; <sup>7</sup>Gene clone libraries. *E. coli*: *Escherichia coli*.

changes in fecal microbiota in cats with chronic diarrhea and their response to dietary modifications<sup>129</sup>. Several bacterial groups correlated with improved fecal scores after therapeutic response to diet. Those included *Slackia* spp., *Campylobacter upsaliensis*, *Enterobacteriaceae* *Raoultella* spp., *Collinsella* spp., and unidentified genera within *Clostridiales* and *Lachnospiraceae*<sup>129</sup>.

More data about the fecal microbiota are available in dogs. In one study, fecal samples from healthy dogs, dogs with acute non-hemorrhagic diarrhea, dogs with acute hemorrhagic diarrhea, and dogs with active or therapeutically controlled idiopathic IBD were analyzed by sequencing of the 16S rRNA gene<sup>141</sup>. Dogs with acute diarrhea, especially those with acute hemorrhagic diarrhea, had the most profound changes in bacterial groups in their microbiome. Dogs with acute hemorrhagic diarrhea had significant decreases in *Blautia*, *Ruminococcaceae* including *Faecalibacterium*, and *Turricibacter* spp., and significant increases in genus *Sutterella* and *C. perfringens* compared to healthy dogs. In another recent study, the fecal microbiome of healthy dogs, dogs with chronic enteropathies, and dogs with acute hemorrhagic diarrhea was evaluated by qPCR assays for selected bacterial groups<sup>155</sup>. The most pronounced changes were decreases in *Faecalibacterium* spp., *Turricibacter* spp., and *Ruminococcaceae* in CE and AHD. *E. coli* and *C. perfringens* were significantly increased in CE and AHD<sup>155</sup>. Especially *Faecalibacterium* spp. is an important group that frequently appears depleted in canine GI disease. This has been confirmed in another study evaluating the fecal microbiota of dogs with idiopathic IBD, in which *Faecalibacterium* spp. was the major bacterial group decreased in diseased dogs<sup>121</sup>. Noteworthy, *Faecalibacterium* spp. correlated with improvement in clinical activity index, suggesting that *Faecalibacterium* spp. may be important for canine GI health, and also may be useful as a monitoring marker for improvement of fecal dysbiosis<sup>14,21</sup>.

While the above discussed studies have reported

changes in microbial groups in GI disease of dogs and cats, only limited information is available about the metabolic consequences that are associated with this dysbiosis, as currently no comprehensive functional studies have been reported in dogs or cats. Alterations in the composition of intestinal microbiota are thought to be an important factor in the pathogenesis of chronic GI diseases. It can be hypothesized that the observed microbiome changes may lead to altered intestinal barrier function, damage to the intestinal brush border and enterocytes, an increased competition for nutrients and vitamins, and to an increased deconjugation of bile acids. Of interest is that commonly depleted groups in GI disease are *Lachnospiraceae*, *Ruminococcaceae*, and *Faecalibacterium*. These bacterial groups, important producers of SCFA, may play an important role in maintenance of gastrointestinal health, as their depletion leads to decreased production of SCFA (e.g., butyrate, acetate), which may impair the capability of the host to down-regulate aberrant intestinal immune response. The importance of some of these bacterial groups that are depleted in IBD have recently been demonstrated in humans. For example, *Faecalibacterium prausnitzii* is consistently reduced in human IBD and this bacterium has been shown to secrete metabolites with anti-inflammatory properties, thereby down-regulating interleukin (IL)-12 and interferon gamma and increasing IL-10 secretions<sup>156</sup>. Disturbances may result in a dysregulation of adaptive immune responses, and lead to inflammation and/or reduced activity against infection. Also, some bacteria produce various toxic agents such as ammonia, D-lactate, endotoxin (LPS), or exotoxin (enterotoxin), and compete for vitamins or other nutrients. Consequently, depletions in serum vitamin B12 concentrations and also increases in serum concentrations of D-lactate are potential consequences of intestinal dysbiosis in cats<sup>157</sup>. However, more comprehensive metabolomics studies are needed in companion animals to elucidate the consequences of

the dysbiosis observed in GI disease.

### Invasive and adherent bacteria

A specific form of colitis occurs in Boxer dogs<sup>[58]</sup> and occasionally also in French Bulldogs<sup>[59]</sup>. This disease is termed granulomatous colitis. Microbiota analysis based on sequencing of 16S rRNA genes in combination with FISH has revealed invasive bacteria in the colonic mucosa of Boxer dogs with granulomatous colitis. Based on comparative 16S rRNA gene analysis, these bacteria have high phylogenetic similarity to *Escherichia coli* (*E. coli*) and *Shigella*. *In situ* analysis with 16S rRNA gene based FISH probes against *E. coli* showed multifocal clusters of invasive bacteria within macrophages in the colonic mucosa<sup>[58]</sup>. The eradication of these invasive *E. coli* in Boxer dogs and French Bulldogs with granulomatous colitis correlates with clinical remission, inferring a causal relationship between these bacteria and the disease<sup>[59]</sup>. Of interest is that these observed phylotypes of *E. coli* isolated from Boxer dogs have high phylogenetic resemblance to *E. coli* associated with Crohn's disease in humans<sup>[16,59]</sup>. The breed specific predisposition of Boxer dogs and French bulldogs to *E. coli* associated granulomatous colitis highly suggests the presence of a genetic susceptibility that impairs their ability to fend off adherent and invasive *E. coli*.

Bacteria invading the intestinal mucosa may also be part of neutrophilic IBD in other dog breeds. Due to the recognized association of granulomatous and neutrophilic IBD with invasive bacteria, specialized testing based on FISH has been developed that allows localizing the bacteria in intestinal biopsies for better guidance of treatment decisions<sup>[59]</sup>.

## ALTERATIONS IN FUNGAL MICROBIOTA

While bacteria are by far the most abundant constituents of the mammalian GI tract, it is now recognized that the gut harbors a highly diverse population of fungal organisms. FISH and shotgun sequencing studies of human and canine fecal DNA have estimated the abundance of fungal organisms and archaea as < 2% of total microbiota<sup>[39,60]</sup>. A recent metagenomic approach estimated that the feline GI microbiota constitutes 0.02% fungi, 0.09% archaea, and 0.09% viruses<sup>[41]</sup>. Fungi were described using pyrosequencing of the fungal 18S rRNA gene in pooled fecal samples of cats<sup>[3]</sup>, with *Aspergillus* and *Saccharomyces* being the most abundant fungal genera. A study reported the prevalence and identification of fungal organisms in the small intestine of healthy dogs and dogs with chronic enteropathies<sup>[61]</sup>. The results indicated a high prevalence (up to 76.1% of dogs) and high diversity of fungal organisms in the canine duodenum. Furthermore, dogs with gastrointestinal disease harbored opportunistic fungal pathogens. A total of 51 different phylotypes were identified, with the most frequently observed phylotypes being *Pichia* spp., *Cryptococcus* spp., *Candida* spp., and *Trichosporon* spp.<sup>[61]</sup>.

A recent study has characterized the fungal micro-

biome (mycobiome) of 19 dogs (12 healthy dogs and 7 dogs with acute diarrhea) using fungal tag-encoded FLX-Titanium amplicon pyrosequencing<sup>[62]</sup>. Five distinct fungal phyla were identified, with *Ascomycota* (median: 97.9% of obtained sequences) and *Basidiomycota* (median 1.0%) being the most abundant. A total of 219 fungal genera were identified across all 19 dogs with a median (range) of 28 (4-69) genera per sample. *Candida* was the most abundant genus found in dogs. However, no significant differences were observed in the relative proportions of fungal communities between healthy and diseased dogs. Therefore, additional studies are needed to elucidate the importance of fungi on intestinal health and disease of animals.

## CONCLUSION

Studies using molecular approaches have provided clear evidence for alterations in microbial communities in the small and large intestine of dogs and cats with GI disorders. However, currently there is a lack of comprehensive studies evaluating the functional consequences of these alterations. A better understanding of these mechanisms will allow for the development of treatment modalities (*e.g.*, prebiotics, probiotics, metabolites) aiming at modulating microbial communities and their produced metabolites. Anecdotal case reports have reported some success using fecal transplantation in dogs with chronic diarrhea. Results of initial studies suggest that the administration of probiotic strains can be useful in dogs with GI disease. For example, probiotic strains have shown benefits in dogs with IBD<sup>[21]</sup>, puppies with acute parvoviral enteritis<sup>[63]</sup>, and adult dogs with non-specific diarrhea<sup>[26,27]</sup>. In cats, probiotics strains have been shown to be beneficial in cats with chronic diarrhea<sup>[28]</sup> and stress-related diarrhea in a shelter environment<sup>[64]</sup>. However, future studies will need to evaluate how these microbial changes impact the immune and metabolic status of dogs and cats.

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