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The role of intestinal bacteria in intestinal health and chronic enteropathies

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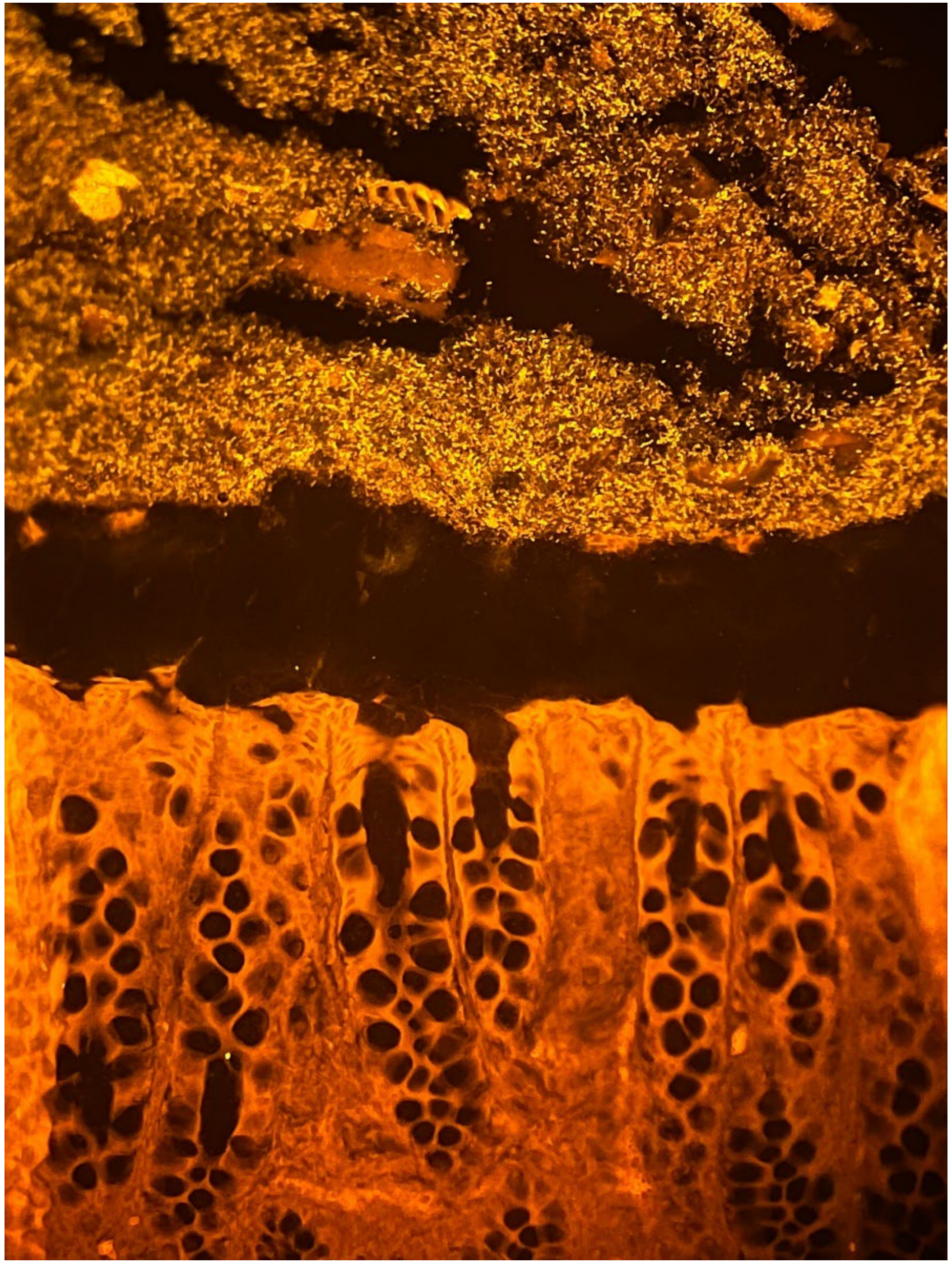
How much do we know about this organ?

This is a <u>metabolic organ</u>

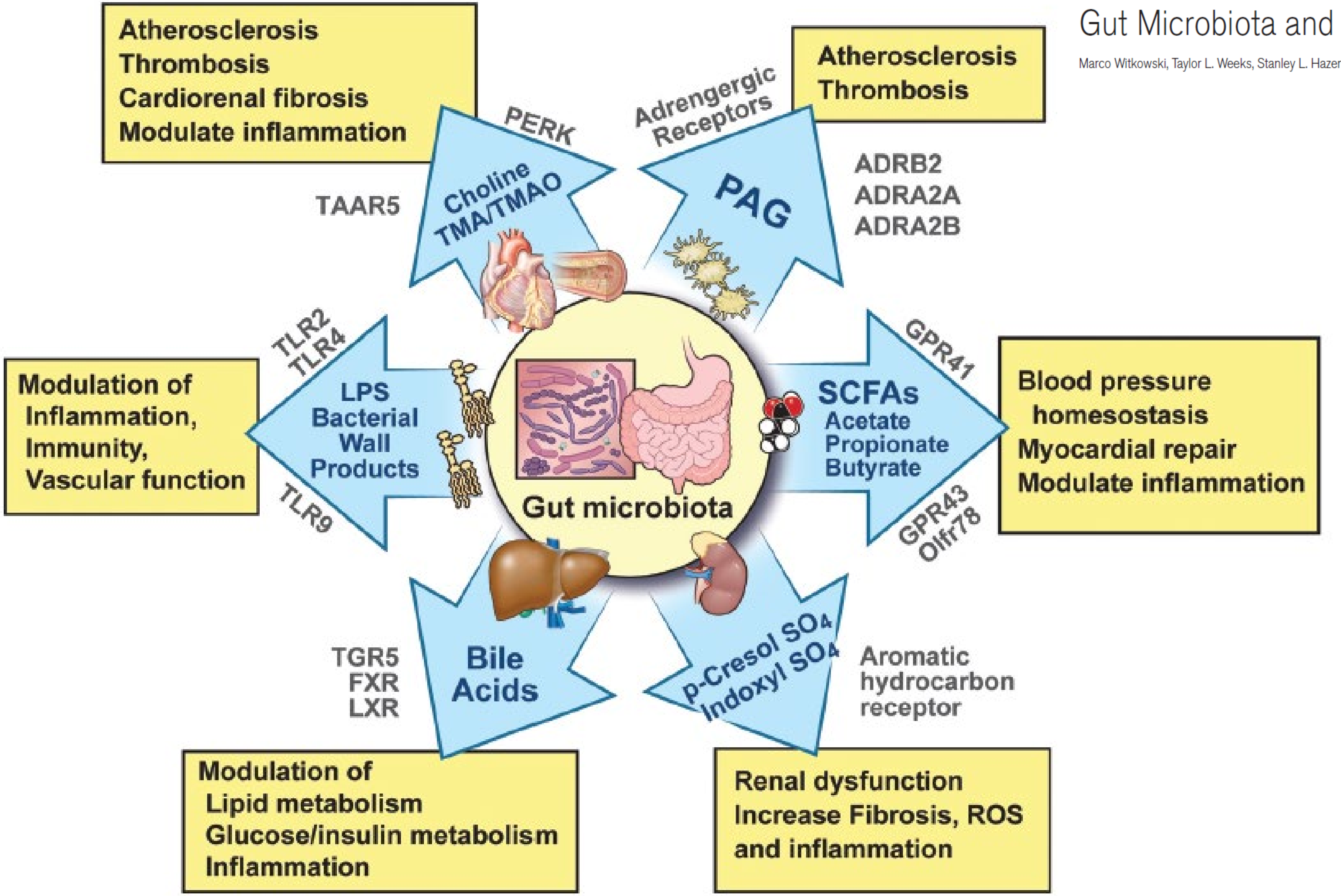
Section through a colon from a cat



Live bacteria (what we see as feces)

Mucus layer

Epitehlium



Circulation Research

REVIEW

Gut Microbiota and Cardiovascular Disease

Marco Witkowski, Taylor L. Weeks, Stanley L. Hazen

MAYO CLINIC
PROCEEDINGS

ORIGINAL ARTICLE | ARTICLES IN PRESS

Association of Infant Antibiotic Exposure With Childhood Health Outcomes

Zaira Aversa, MD, PhD • Elizabeth J. Atkinson, MS • Marissa J. Schafer, PhD • ... Walter A. Rocca, MD • Martin J. Blaser, MD • Nathan K. LeBrasseur, PhD • Show all authors

Published: November 15, 2020 • DOI: https://doi.org/10.1016/j.mayocp.2020.07.019

broad spectrum antibiotics

- 14,572 children (7026 girls and 7546 boys)
  - 70% (10,220) received at least 1 antibiotic prescription during the first 2 years of life.

- Early antibiotic exposure associated with increased risk:
  - childhood-onset asthma
  - allergic rhinitis
  - atopic dermatitis
  - hazard ratios ranging from 1.20 to 2.89

OUTLINE

- microbial metabolites and immunity
  - short chain fatty acids
  - Intestinal bile acids
  - tryptophan/indole
- causes for dysbiosis
  - dietary causes (low fiber)
  - intestinal inflammation
  - antibiotics

Source	Bacteria involved	Microbial metabolite(s)	Effects in host	
			beneficial (in normal concentrations)	**potentially deleterious (in abnormal concentrations)**
carbohydrates from diet	various (e.g. Faecalibacterium, Turicibacter)	fermentation to short-chain fatty acids (SCFA)	anti-inflammatory maintain intestinal barrier function	abnormal SCFA ratio can activate virulence factors of enteropathogens

Ziese AL, Suchodolski JS. Impact of Changes in Gastrointestinal Microbiota in Canine and Feline Digestive Diseases. Vet Clin Small Anim, 2021

The canine Core Microbiome based on DNA shotgun sequencing

@taz_species_level	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9	Dog 10	Dog 11	Dog 12	Cour
s__Other	18.0%	21.2%	18.7%	19.3%	14.3%	30.9%	28.9%	40.1%	35.2%	14.3%	14.8%	14.2%	12
s__[Ruminococcus]_gnavus	3.7%	1.7%	23.5%	5.6%	1.4%	3.6%	2.7%	12.3%	1.4%	2.5%	8.3%	3.4%	12
s__[Clostridium]_hiranonis	10.2%	16.0%	0.8%	3.4%	0.7%	17.3%	0.7%	0.0%	1.8%	0.4%	0.3%	8.1%	12
s__Clostridium_sp._AT4	1.0%	0.5%	0.8%	0.1%	0.8%	3.0%	3.3%	2.6%	1.0%	0.8%	7.3%	0.4%	12
s__Blautia_wexlerae	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	5.9%	6.0%	0.6%	1.4%	0.0%	0.1%	12
s__Blautia_hansenii	[illegible]	2.8%	0.9%	2.8%	0.5%	2.2%	0.2%	0.6%	0.7%	0.3%	0.6%	1.3%	12
s__Faecalibacterium_prausnitzii	1.8%	2.2%	0.7%	0.0%	2.6%	0.2%	0.6%	0.0%	2.3%	2.7%	0.0%	0.0%	12
s__Bacteroides_coprocola	0.1%	0.3%	0.8%	0.2%	1.7%	0.2%	1.2%	0.3%	2.0%	0.8%	2.9%	0.0%	12
s__Fournierella_massiliensis	0.1%	0.8%	0.4%	0.0%	0.4%	0.2%	0.2%	0.1%	1.1%	3.9%	3.0%	0.0%	12
s__Coprococcus_sp._HPP0074	0.9%	0.4%	1.1%	0.8%	0.2%	1.4%	0.1%	0.1%	0.2%	0.1%	0.0%	0.8%	12
s__Bacteroides_plebeius	0.0%	[illegible]	[illegible]	0.1%	0.0%	0.3%	0.5%	0.0%	1.0%	2.9%	0.0%	0.0%	12
s__Butyricicoccus_pullicaecorum	0.2%	0.0%	0.6%	0.2%	0.6%	0.5%	0.3%	0.6%	0.2%	0.9%	0.6%	0.0%	12
s__Flavonifractor_plautii	0.1%	0.1%	0.0%	[illegible]	0.1%	0.0%	0.0%	3.1%	0.1%	0.1%	0.0%	0.0%	12
s__[Clostridium]_glycyrrhizinilyticum	0.5%	0.2%	0.2%	0.1%	0.1%	0.3%	0.0%	1.2%	0.1%	0.1%	0.2%	0.5%	12
s__Blautia_sp._Marseille-P3201T	0.4%	0.5%	[illegible]	0.9%	0.2%	0.5%	0.1%	0.2%	0.2%	0.1%	0.1%	0.2%	12
s__Holdemanella_biformis	0.3%	0.4%	0.0%	[illegible]	0.1%	0.9%	0.8%	0.0%	0.2%	0.1%	0.0%	0.0%	12
s__Bacteroides_stercoris	0.0%	0.0%	0.0%	1.9%	0.3%	0.0%	0.0%	0.0%	0.1%	0.1%	0.2%	0.0%	12
s__Coprococcus_sp._HPP0048	0.4%	0.2%	0.4%	0.4%	0.1%	[illegible]	0.1%	0.0%	0.1%	0.0%	0.0%	0.3%	12
s__Tyzzerella_nexilis	0.1%	0.1%	0.0%	0.2%	0.0%	0.1%	0.0%	1.8%	0.0%	0.0%	0.2%	0.1%	12
s__Blautia_obeum	0.2%	0.1%	0.1%	0.0%	0.1%	0.1%	[illegible]	0.7%	0.1%	0.2%	0.0%	0.1%	12
s__Absiella_dolichum	0.2%	0.1%	0.0%	0.7%	0.0%	[illegible]	0.0%	0.1%	0.1%	0.0%	0.0%	0.1%	12
s__[Eubacterium]_hallii	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	0.0%	0.0%	0.0%	0.0%	0.0%	12
s__Blautia_massiliensis	0.2%	0.2%	0.2%	0.1%	0.2%	[illegible]	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	12
s__Bacteroides_fragilis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	12
s__Collinsella_intestinalis	34.3%	21.3%	33.7%	59.4%	20.6%	18.7%	4.0%	0.0%	[illegible]	20.8%	48.5%	55.8%	11
s__Prevotella_copri	9.6%	8.3%	5.8%	0.0%	44.5%	7.3%	[illegible]	7.9%	9.8%	38.5%	3.7%	0.0%	11
s__Allobaculum_stercoricanis	9.3%	10.5%	7.5%	1.9%	2.4%	0.0%	0.3%	0.0%	4.5%	[illegible]	1.8%	8.0%	11
s__Catenibacterium_mitsuokai	0.0%	0.4%	0.0%	0.0%	0.0%	4.8%	0.7%	0.0%	[illegible]	0.1%	0.0%	0.0%	11
s__Collinsella_phocaeensis	0.1%	0.4%	0.2%	0.2%	0.7%	0.1%	0.2%	0.0%	0.4%	1.2%	0.2%	0.2%	11
s__Sutterella_wadsworthensis	0.1%	0.2%	0.2%	0.0%	0.8%	0.3%	0.4%	0.3%	0.1%	0.7%	0.0%	0.0%	11
s__Collinsella_stercoris	0.2%	0.2%	0.3%	0.3%	0.2%	0.2%	0.0%	0.0%	[illegible]	0.2%	0.4%	0.5%	11
s__Megamonas_funiformis	0.1%	0.2%	0.0%	0.0%	0.1%	0.6%	1.8%	0.0%	0.1%	0.4%	0.3%	[illegible]	10
s__Sutterella_sp._KLE1602	0.1%	0.2%	0.1%	0.0%	0.9%	0.3%	0.4%	0.3%	0.1%	0.7%	[illegible]	0.0%	10
s__Megamonas_sp._Calf98-2	0.1%	0.2%	0.0%	0.0%	0.0%	0.4%	1.0%	0.0%	0.0%	[illegible]	0.2%	0.0%	10
s__Slackia_piriformis	0.9%	0.1%	0.5%	0.0%	0.6%	0.0%	0.1%	0.0%	0.8%	0.6%	0.0%	0.0%	9
s__Escherichia_coli	0.0%	0.1%	0.0%	0.0%	0.0%	0.4%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	9
s__Lactococcus_lactis	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	7
s__Clostridium_perfringens	0.0%	4.2%	0.0%	0.0%	0.0%	0.5%	0.0%	0.0%	0.0%	0.3%	0.0%	0.3%	6
s__Streptococcus_infantarius	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%	0.0%	0.1%	0.0%	6
s__Lactobacillus_delbrueckii	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	6
s__bacterium_LF-3	0.0%	0.1%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	6
s__Streptococcus_gallolyticus	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.0%	1.8%	0.0%	5
s__Lactobacillus_sakei	0.0%	0.0%	0.0%	0.0%	0.1%	0.4%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	5
s__Bifidobacterium_kashiwanohense	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	5
s__Streptococcus_lutetiensis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	4.6%	0.0%	0.5%	0.0%	4
s__Anaerobiospirillum_succiniciproducens	0.0%	1.4%	0.0%	0.0%	0.8%	0.0%	0.0%	0.0%	1.3%	0.0%	0.0%	0.0%	4
s__Streptococcus_thermophilus	2.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	4
s__Lactococcus_piscium	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	4
s__Bifidobacterium_pseudocatenulatum	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	14.5%	0.0%	0.0%	0.0%	0.0%	0.0%	3
s__Eggerthella_lenta	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.1%	0.0%	0.0%	0.0%	0.0%	3
s__Lactococcus_garvieae	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3
s__Propionibacterium_freudenreichii	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.3%	2
s__Bilophila_wadsworthia	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	2
s__Bifidobacterium_catenulatum	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	2
s__Enterococcus_hirae	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2
s__Lactobacillus_mucosae	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2
s__Sellimonas_intestinalis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	13.9%	0.0%	0.0%	0.0%	0.0%	1
s__Bifidobacterium_gallinarum	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	1
s__Lactococcus_sp._DD01	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1
s__Lactobacillus_animalis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1
s__Providencia_alcalifaciens	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0
s__Staphylococcus_succinus	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0

- 1,065 bacteria species identified across 12 healthy dogs

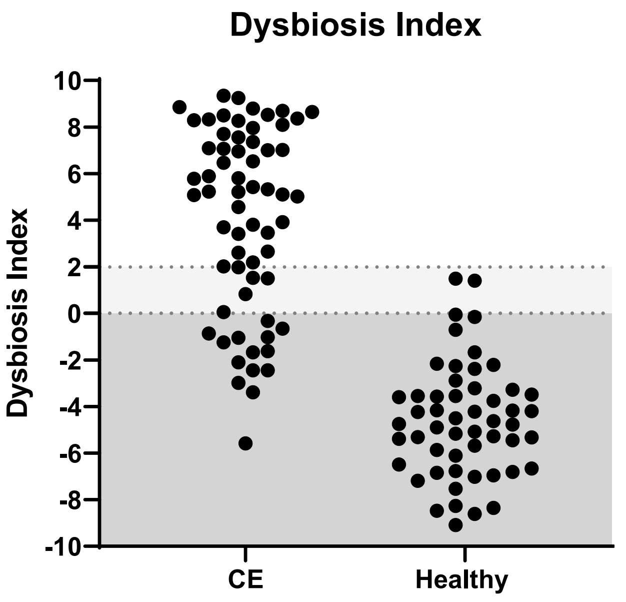
- 25 identified in all 12/12 dogs
- 36 identified in 9/12 dogs

- top Core species and genera include
  - *Clostridium hiranonis*
  - *Blautia*
  - *Faecalibacterium*

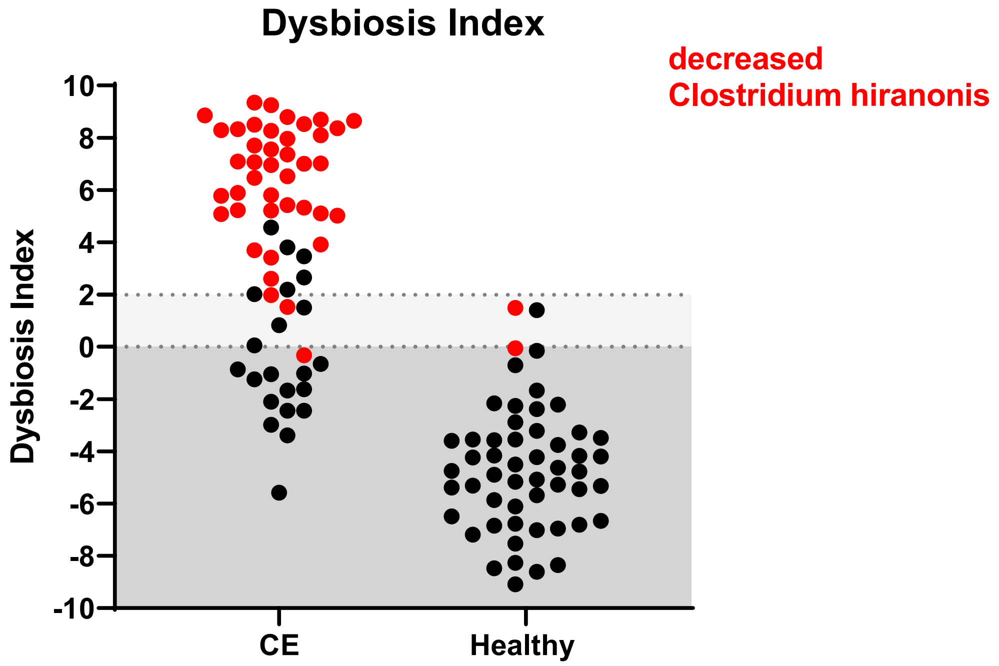
RESEARCH ARTICLE

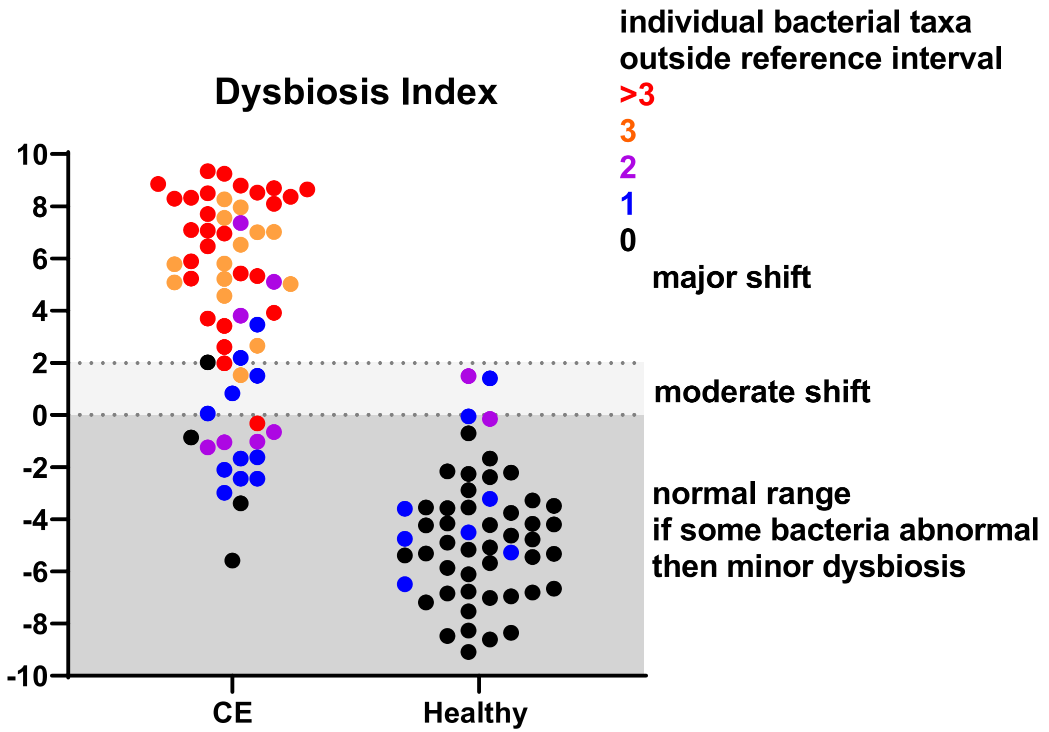
A dysbiosis index to assess microbial changes in fecal samples of dogs with chronic inflammatory enteropathy

MK AlShawaqfeh[1,2], B Wajid[1,3], Y Minamoto[1], M Markel[1], JA Lidbury[1], JM Steiner[1], E Serpedin[2] and JS Suchodolski[1,*]



	Change in dysbiosis	Properties
beneficial		
Faecalibacterium	↓	anti-inflammatory
Turicibacter	↓	short-chain fatty acids
Blautia	↓	short-chain fatty acids
Fusobacterium	↓	short-chain fatty acids
Clostridium hiranonis	↓	bile acid converter
harmful		
Streptococcus	↑	overgrowth in maldigestion
E. coli	↑	pro-inflammatory

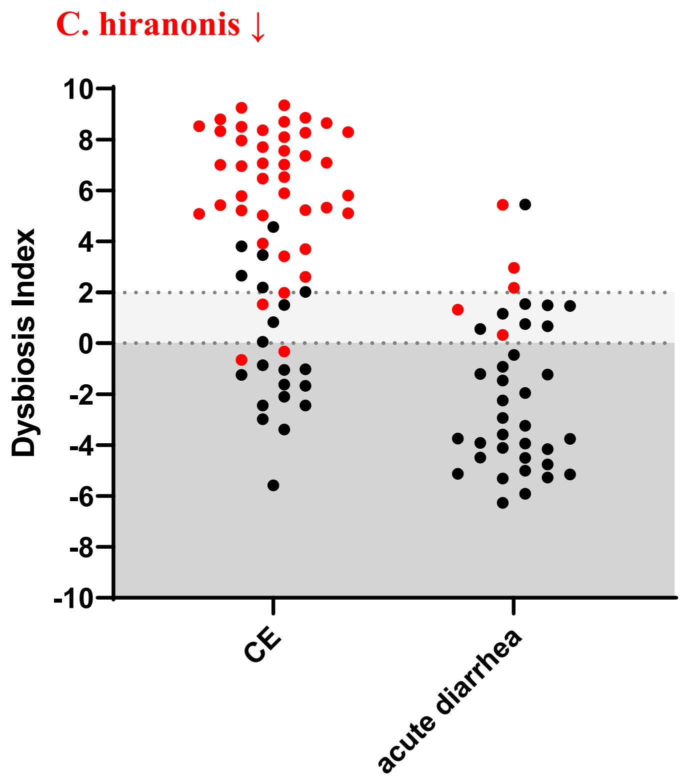




Dysbiosis Index		Sensitivity	CI (95%)		Specificity	CI (95%)
2		0.63	0.53-0.72		1	0.96-1.00
0		0.74	0.65-0.82		0.95	0.89-0.98
-1		0.82	0.73-0.88		0.91	0.84-0.96
-2		0.86	0.78-0.92		0.83	0.74-0.90

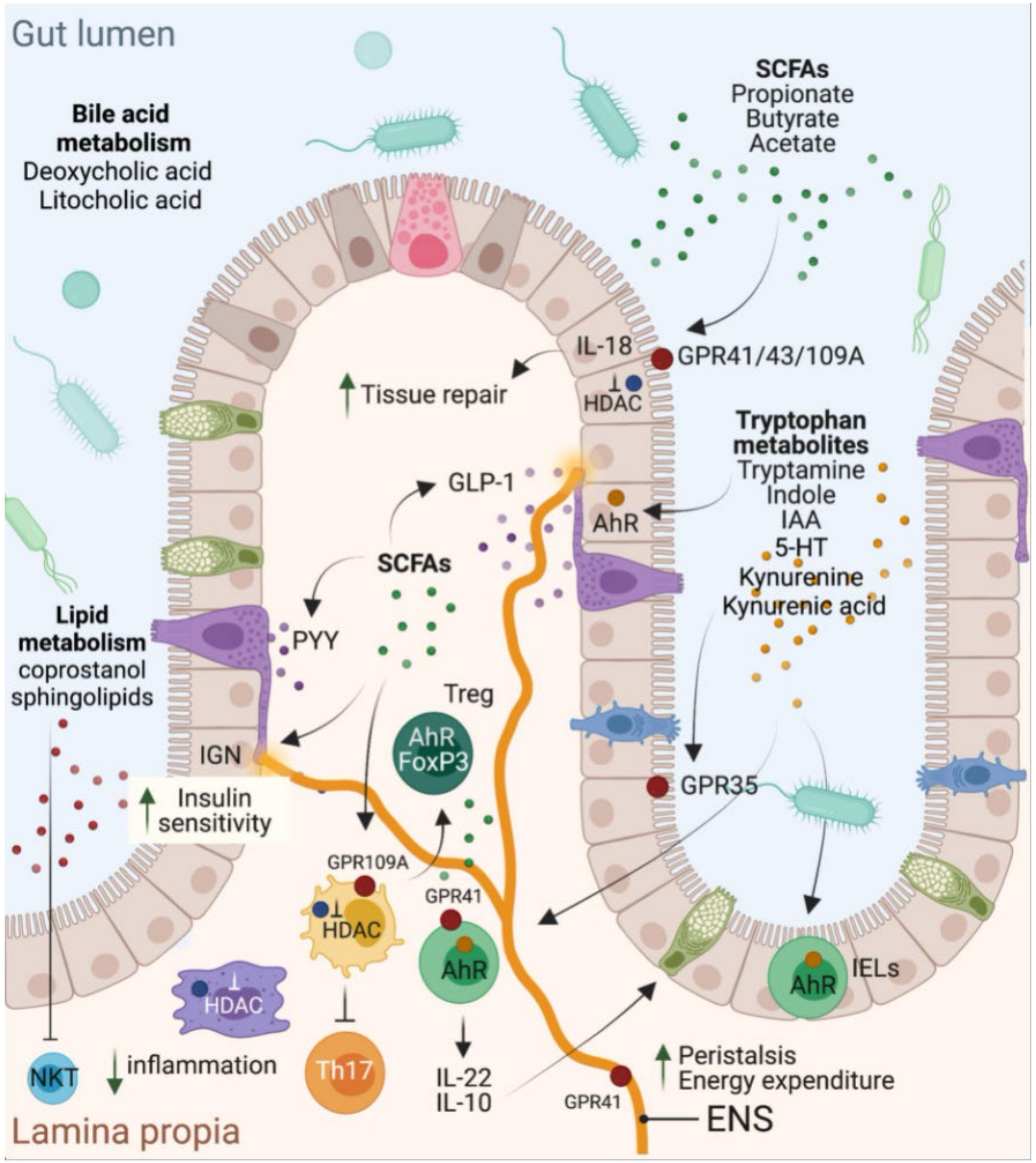
Dysbiosis patterns vary across GI disease

- dogs with chronic diarrhea
  - food-responsive
  - antibiotic-responsive
  - idiopathic IBD
  - exocrine pancreatic insufficiency (EPI)



- acute diarrhea
  - rarely increased DI and decreased C. hiranonis

- antibiotic-induced dysbiosis: should be off antibiotics for 2-4 weeks
- omeprazole-induced dysbiosis: should be off omeprazole for 10-14 days



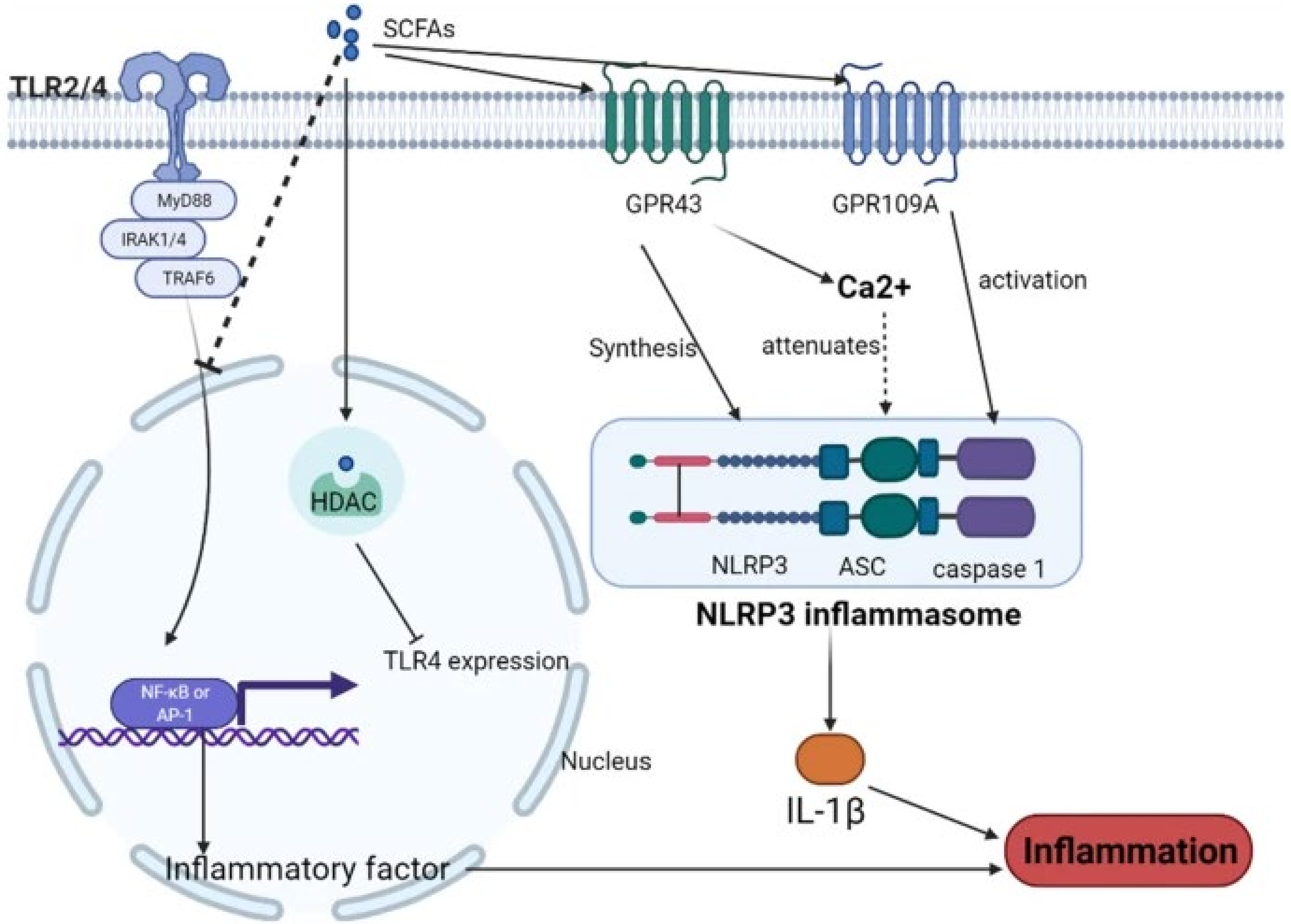
Next Generation Microbiome Research: Identification of Keystone Species in the Metabolic Regulation of Host-Gut Microbiota Interplay

Héloïse Tudela[1,2], Sandrine P. Claus[1*] and Maya Saleh[2,3*]

Short-chain fatty acids (SCFA)

- produced from dietary fiber
- signal through G-receptors
  - IL-18 production which is required for intestinal epithelial integrity
  - anti-inflammatory

Important bacterial keystone species: **Faecalibacterium**



- SCFAs inhibit progression of IBD by regulating Toll-like receptors (TLRs) and NLRP3 inflammasomes

- SCFAs suppress histone acetylation pathway

Regulatory role of short-chain fatty acids in inflammatory bowel disease

Zhilin Zhang, Huan Zhang, Tian Chen, Lin Shi, Daorong Wang & Dong Tang

Cell Communication and Signaling **20**, Article number: 64 (2022) | Cite this article

ORIGINAL ARTICLE

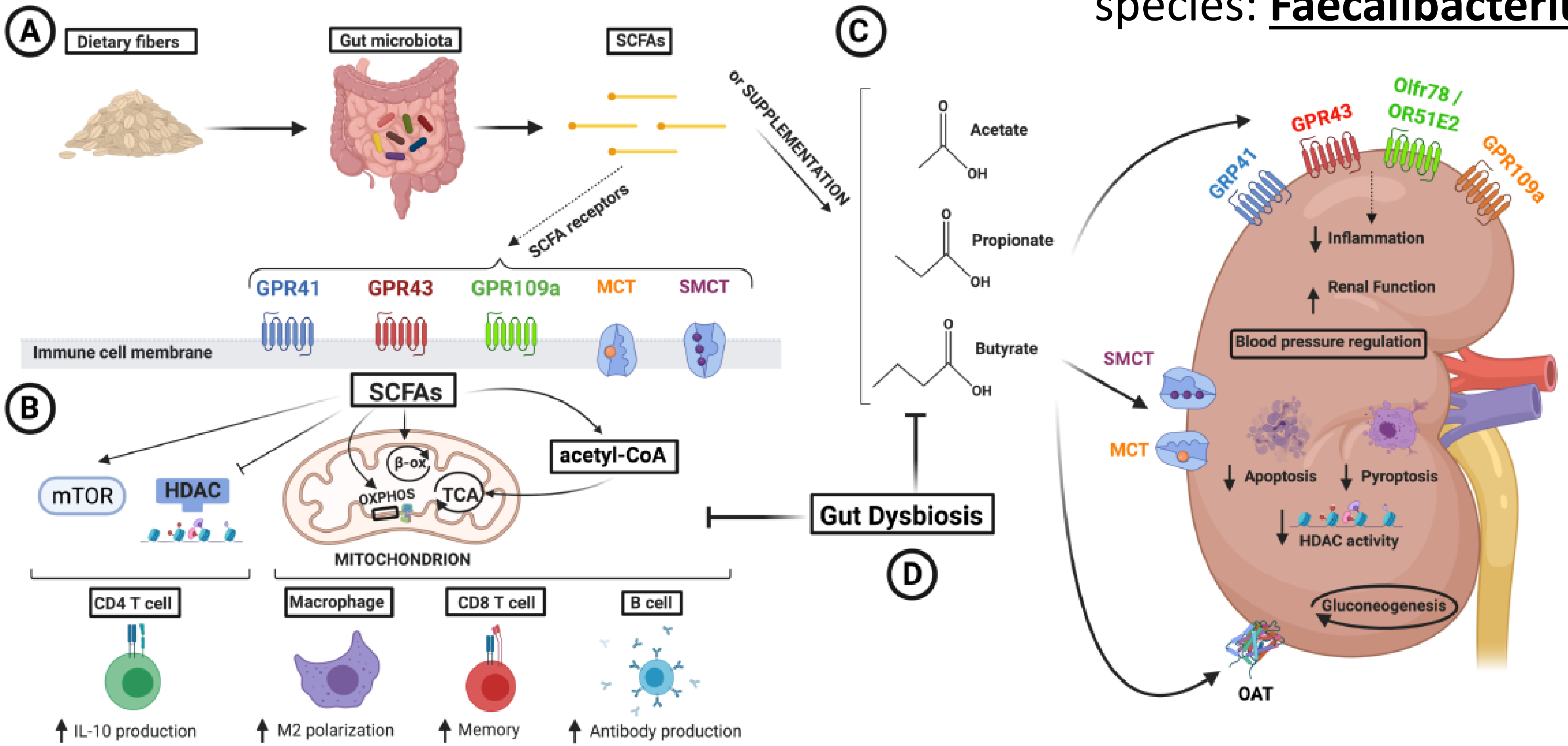
Schaubeck M, *et al*. *Gut* 2015;**0**:1–13. doi:10.1136/gutjnl-2015-309333

Dysbiotic gut microbiota causes transmissible Crohn's disease-like ileitis independent of failure in antimicrobial defence

Conclusions We provide clear experimental evidence for the causal role of gut bacterial dysbiosis in the development of chronic ileal inflammation with subsequent failure of Paneth cell function.

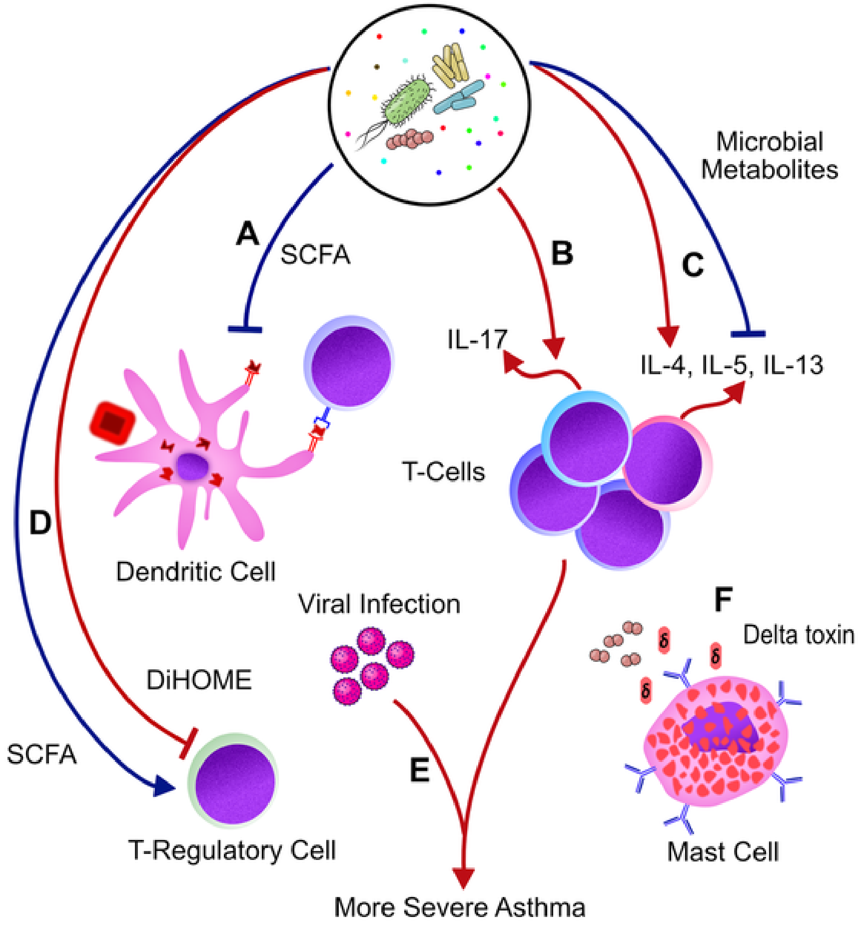
Dysbiosis can trigger inflammation, but other co-factors are needed

Important bacterial keystone species: **Faecalibacterium**



Foresto-Neto et al, Renal sensing of bacterial metabolites in the gut-kidney axis. Kidney360 (Am Soc Nephrology) 2021

- **Bacteria and metabolites impact multiple stages in the well-established pathway of allergic inflammation**
  - **protective effects (blue arrows)**
  - **exacerbating allergic inflammation (red arrows)**



Wilson NG, Hernandez-Leyva A, Kau AL (2019) The ABCs of wheeze: Asthma and bacterial communities. PLOS Pathogens 15(4): e1007645. https://doi.org/10.1371/journal.ppat.1007645

SHORT CHAIN FATTY ACIDS

Direct and indirect regulation of enteropathogens by SCFAs

2. activation of virulence genes of enteropathogens

- increasing concentration of acetate in distal ileum

→ signal for invasion gene expression by production of acetyl-phosphate in bacterial cytoplasm

→ pathway bypasses barA

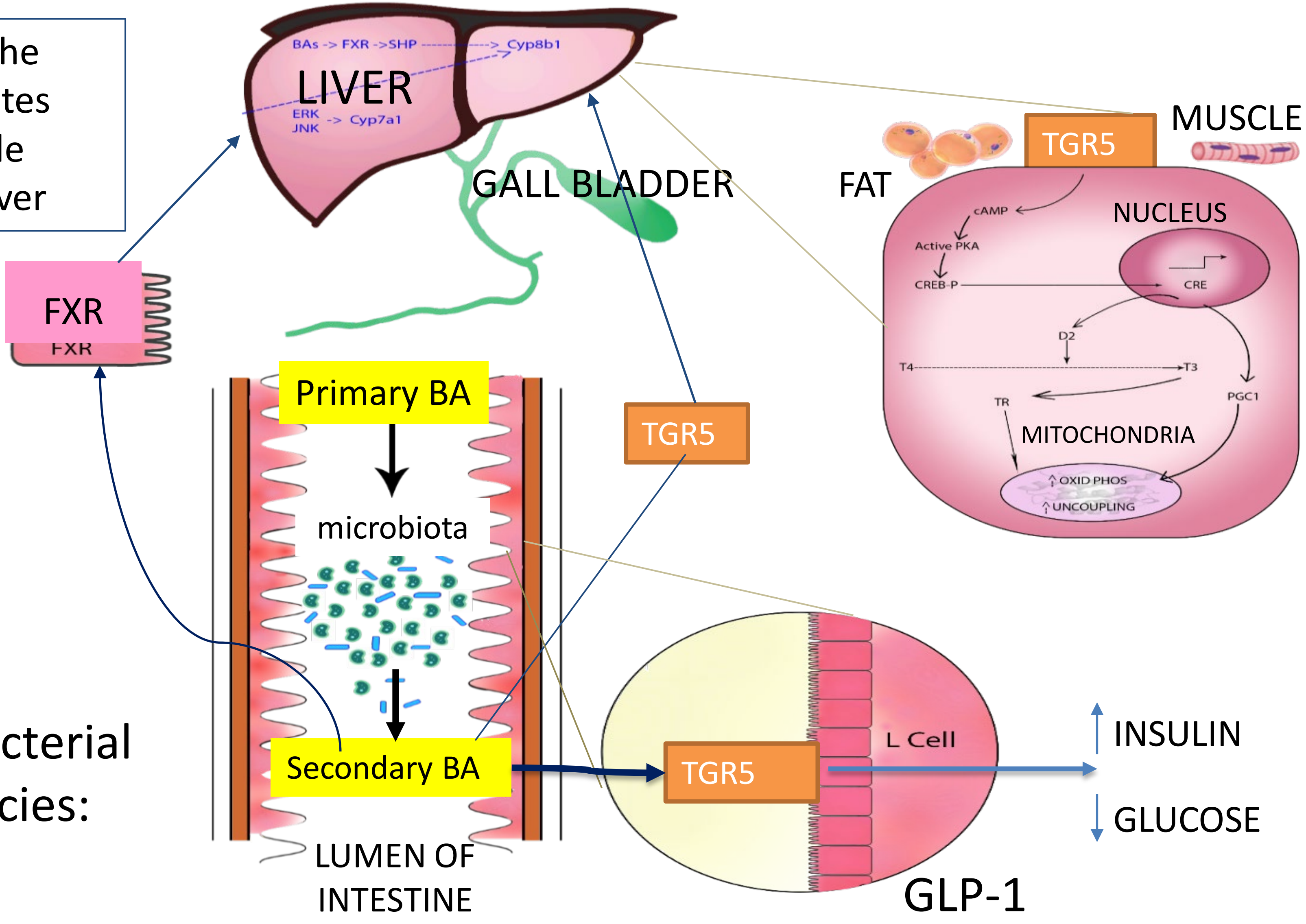
- propionate and butyrate, present in high concentrations in caecum and colon reduce expression in wild-type strain

→ alterations in SCFA concentrations and ratios that favor acetate and decrease propionate and butyrate might make *Salmonella* more invasive

Lawhon et al., Mol Microbiol, 2002

Microbial conversion of primary to secondary bile acids is important for health

Feedback from the intestines regulates production of bile acids from the liver



Secondary bile acids inhibit pro-inflammatory cytokines (TNF-α, IL-6)

Secondary BA inhibit *C. difficile*

Primary BA promote *C. difficile*

Important bacterial keystone species: **Clostridium hiranonis**

Pharmacological Research
Volume 104, February 2016, Pages 9-21

Invited review

Pharmacology of bile acid receptors: Evolution of bile acids from simple detergents to complex signaling molecules

Bryan L. Copple[a], Tiangang Li[b]

Physiological Functions of Bile Acid Receptors

Bile Acid Receptors

Farnesoid X Receptor
Vitamin D Receptor
Pregnane X Receptor
TGR5
α1β5 Integrin
Sphingosine-1-phosphate Receptor 2

Bile acid synthesis, transport, and detoxification

Choleresis

Glucose homeostasis

Lipid metabolism

Gastric motility

Cholangiocyte proliferation and survival

Gallbladder filling

Energy expenditure

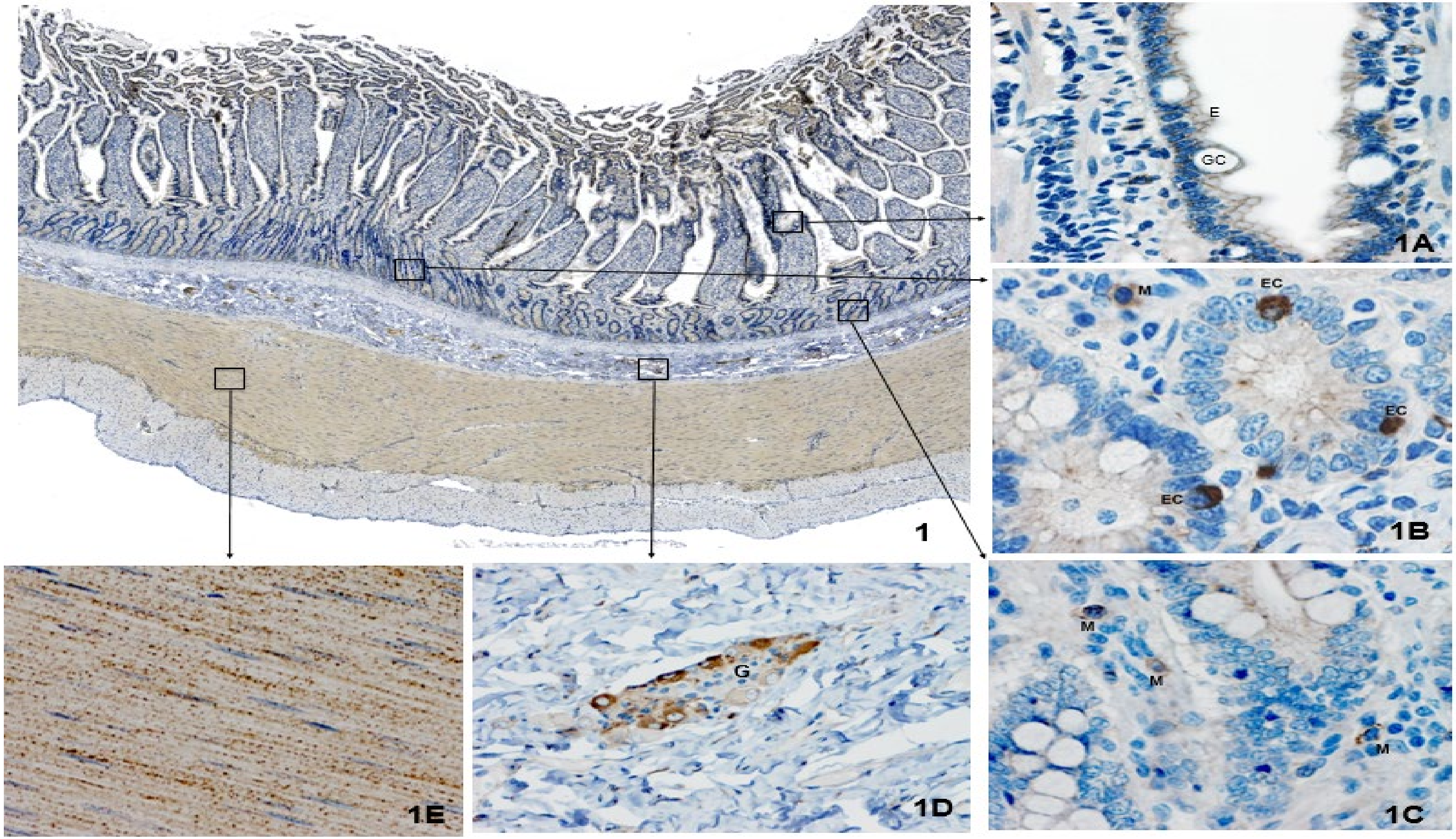
Pruritis

Immunomodulation

TGR5 BILE ACID RECEPTORS IN SMALL AND LARGE INTESTINE OF HEALTHY DOGS

Giaretta et al, Histology and Histopathology 2019

GC= goblet cell; C= colonocyte; M= macrophage; EC= enteroendocrine cell; G= ganglion cell; En= endothelial cell.



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Article | Published: 16 March 2022

Human gut bacteria produce T_H17-modulating bile acid metabolites

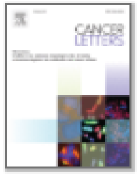
Donggi Paik, Lina Yao, Yancong Zhang, Sena Bae, Gabriel D. D'Agostino, Minghao Zhang, Eunha Kim, Eric

- gut bacteria convert secondary bile acid lithocholic acid into 3-oxoLCA and isolithocholic acid (isoLCA)
- suppressed T_H17 cell differentiation by inhibiting retinoic acid receptor-related orphan nuclear receptor-γt
- levels significantly reduced in IBD
- data suggest that bacterially produced bile acids inhibit T_H17 cell function, an activity that may be relevant to the pathophysiology of IBD

Article Advance

Cancer Letters

Volume 412, 1 January 2018, Pages 194-207



Original Article

The membrane bile acid receptor TGR5 drives cell growth and migration via activation of the JAK2/STAT3 signaling pathway in non-small cell lung cancer

Highlights

- Overexpression of TGR5 predicts poor prognosis in NSCLC patients in combination with p-STAT3 (at Tyr705) expression.
- TGR5 promotes cell proliferation, migration and invasion via activation of JAK2/STAT3 signaling pathway in NSCLC.
- Bile acids may appear to be a major etiologic factor in lung carcinogenesis by activating the TGR5 receptor.

Open Access | Published: 19 July 2016

Bile signalling promotes chronic respiratory infections and antibiotic tolerance

F. Jerry Reen, Stephanie Flynn, David F. Woods, Niall Dunphy, Muireann Ní Chróinín, David Mullane, Stephen Stick, Claire Adams & Fergal O'Gara

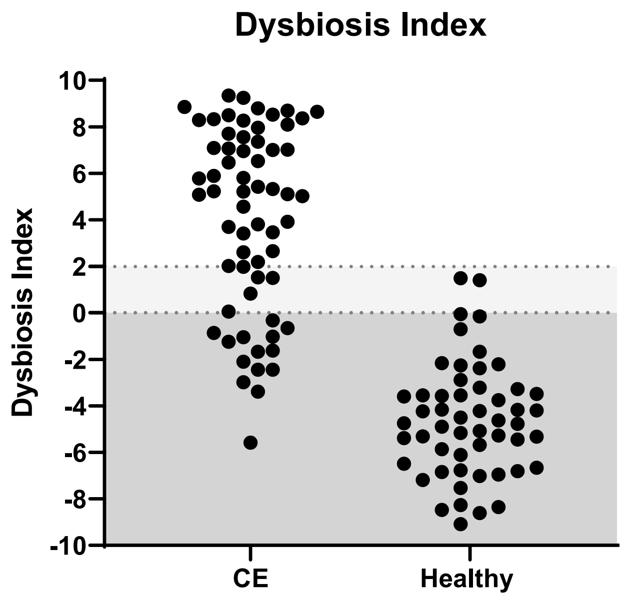
Scientific Reports **6**, Article number: 29768 (2016) | Cite this article

- bile aspiration?
- chenodeoxycholic acid (CDCA) induced pro-inflammatory Interleukin-6 in lung epithelial cells
    - Farnesoid X Receptor (FXR) dependent
- suggest bile acid signalling a trigger for development of chronic respiratory disease

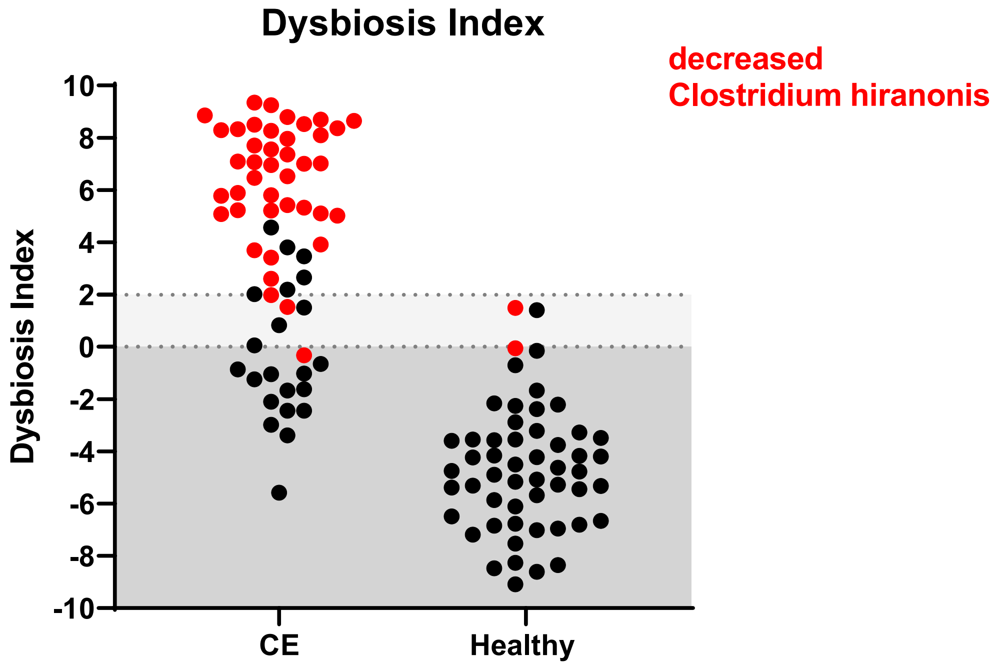
RESEARCH ARTICLE

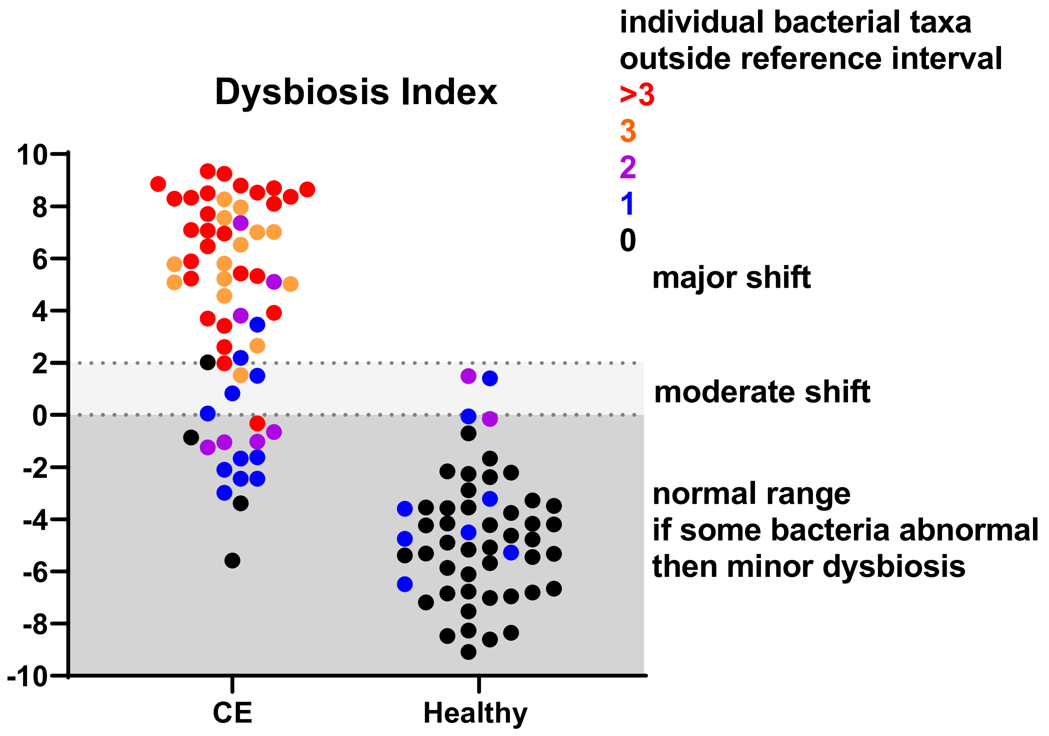
A dysbiosis index to assess microbial changes in fecal samples of dogs with chronic inflammatory enteropathy

MK AlShawaqfeh[1,2], B Wajid[1,3], Y Minamoto[1], M Markel[1], JA Lidbury[1], JM Steiner[1], E Serpedin[2] and JS Suchodolski[1,*]

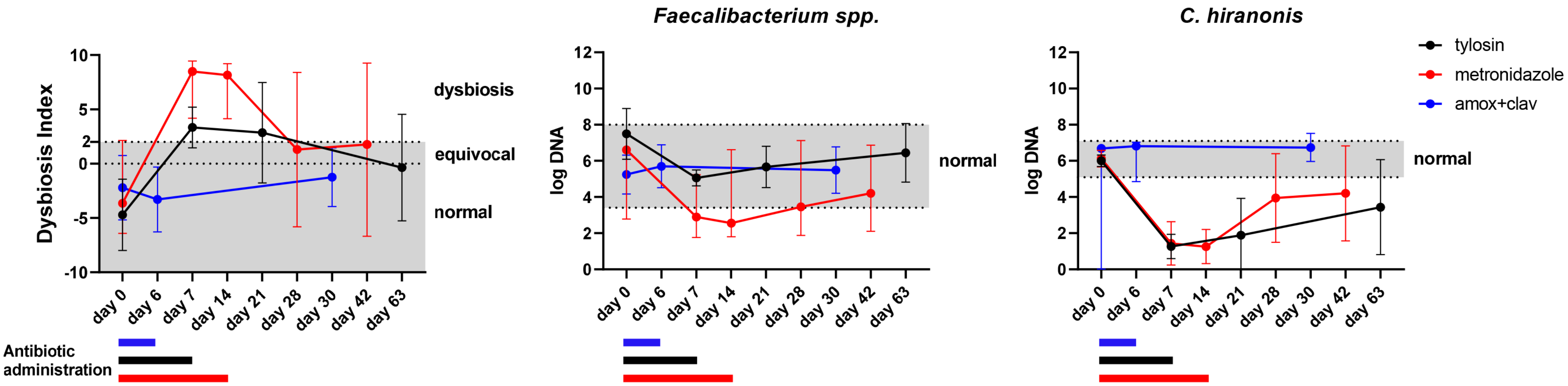


	Change in dysbiosis	Properties
beneficial		
Faecalibacterium	↓	anti-inflammatory
Turicibacter	↓	short-chain fatty acids
Blautia	↓	short-chain fatty acids
Fusobacterium	↓	short-chain fatty acids
Clostridium hiranonis	↓	bile acid converter
harmful		
Streptococcus	↑	overgrowth in maldigestion
E. coli	↑	pro-inflammatory





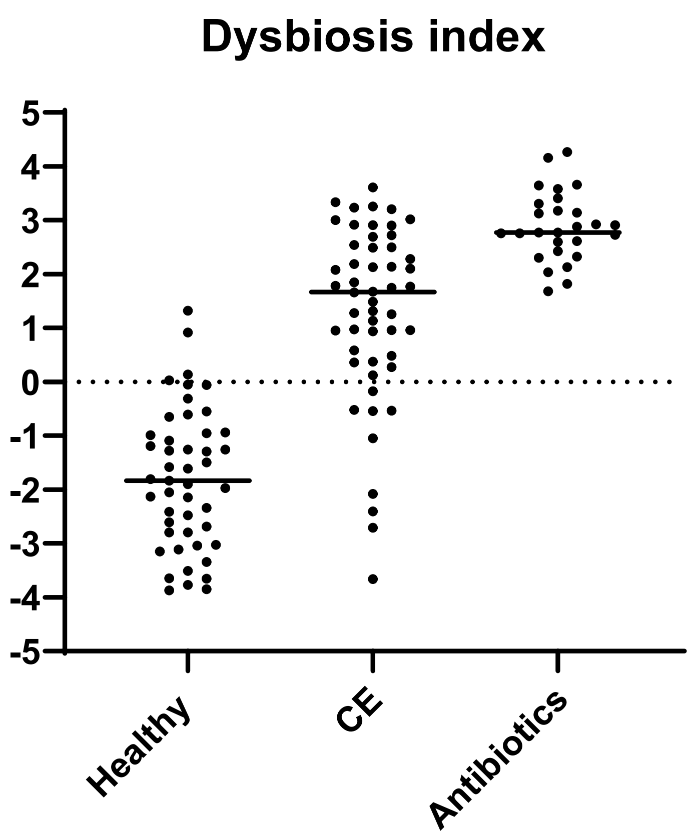
Dysbiosis Index		Sensitivity	CI (95%)		Specificity	CI (95%)
2		0.63	0.53-0.72		1	0.96-1.00
0		0.74	0.65-0.82		0.95	0.89-0.98
-1		0.82	0.73-0.88		0.91	0.84-0.96
-2		0.86	0.78-0.92		0.83	0.74-0.90



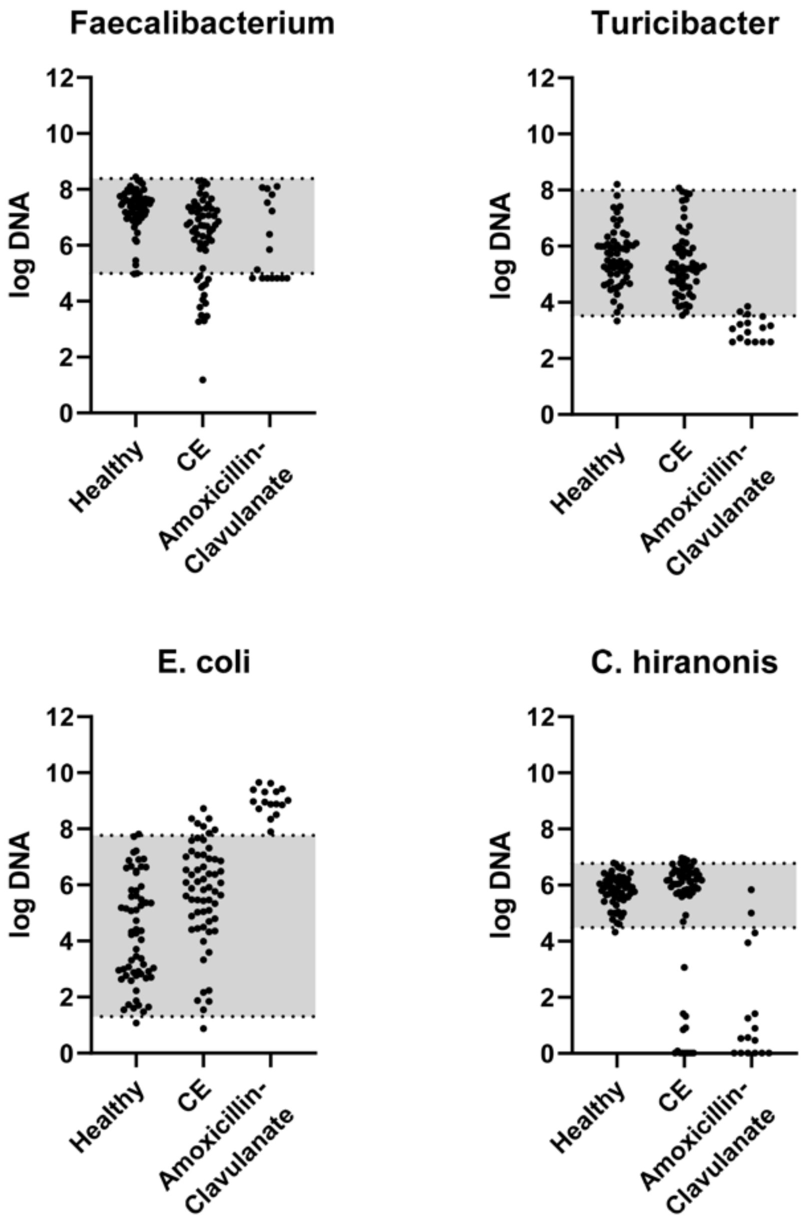
Suchodolski JS. Analysis of the Gut Microbiota, Vet Clin Path 2021

Examples for dysbiosis in cats

- chronic enteropathies (CE) and antibiotics
- reduction in SCFA producing bacteria
  - Faecalibacterium
  - Turicibacter
- increase in TMAO producing bacteria
  - E. coli



DI < 0 normal
DI > 0 dysbiosis

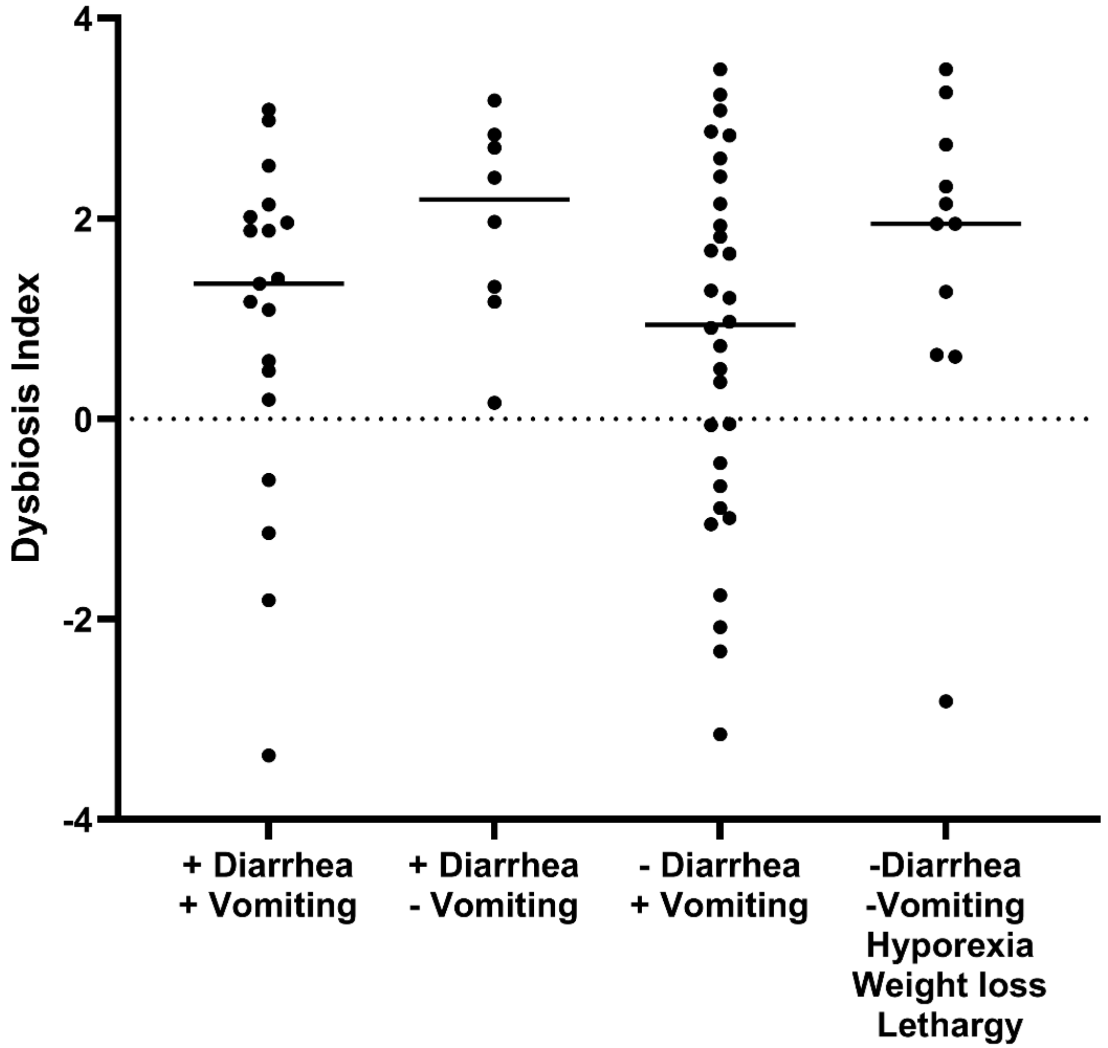


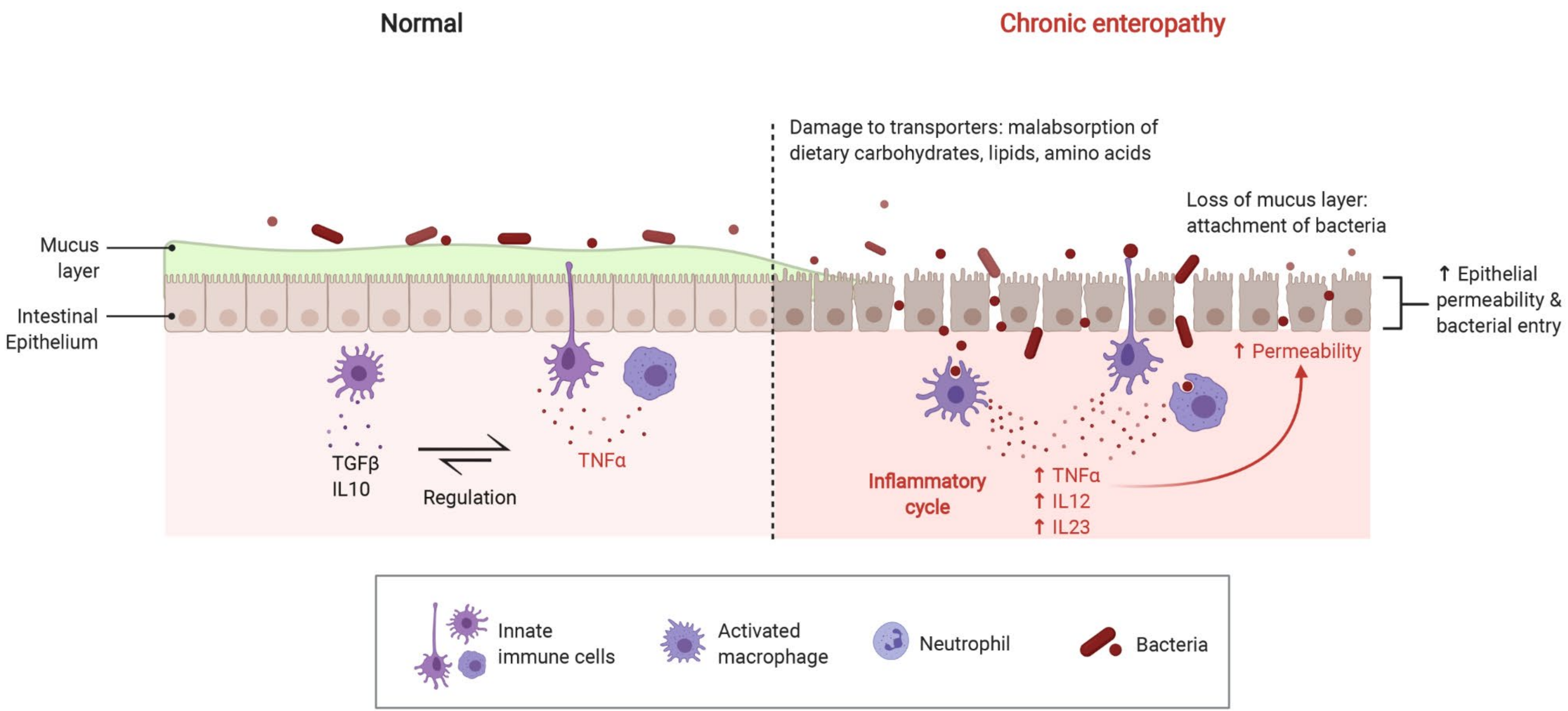
grey zone = reference interval

Result - Clinicopathological findings of cats with CE

Variables	number (%)	total number evaluated
increased dysbiosis index (>0)	52 (76%)	68
decreased serum cobalamin (<290 ng/L)	21 (34%)	61
increased serum folate (>21.6 µg/L)	15 (28%)	53
increased fPLI (>3.5 µg/L)	14 (28%)	50
increased fTLI (>82 µg/L)	10 (21%)	47
decreased serum folate (<9.7 µg/L)	6 (11%)	53
decreased serum albumin (<2.5 g/dL)	2 (4%)	53

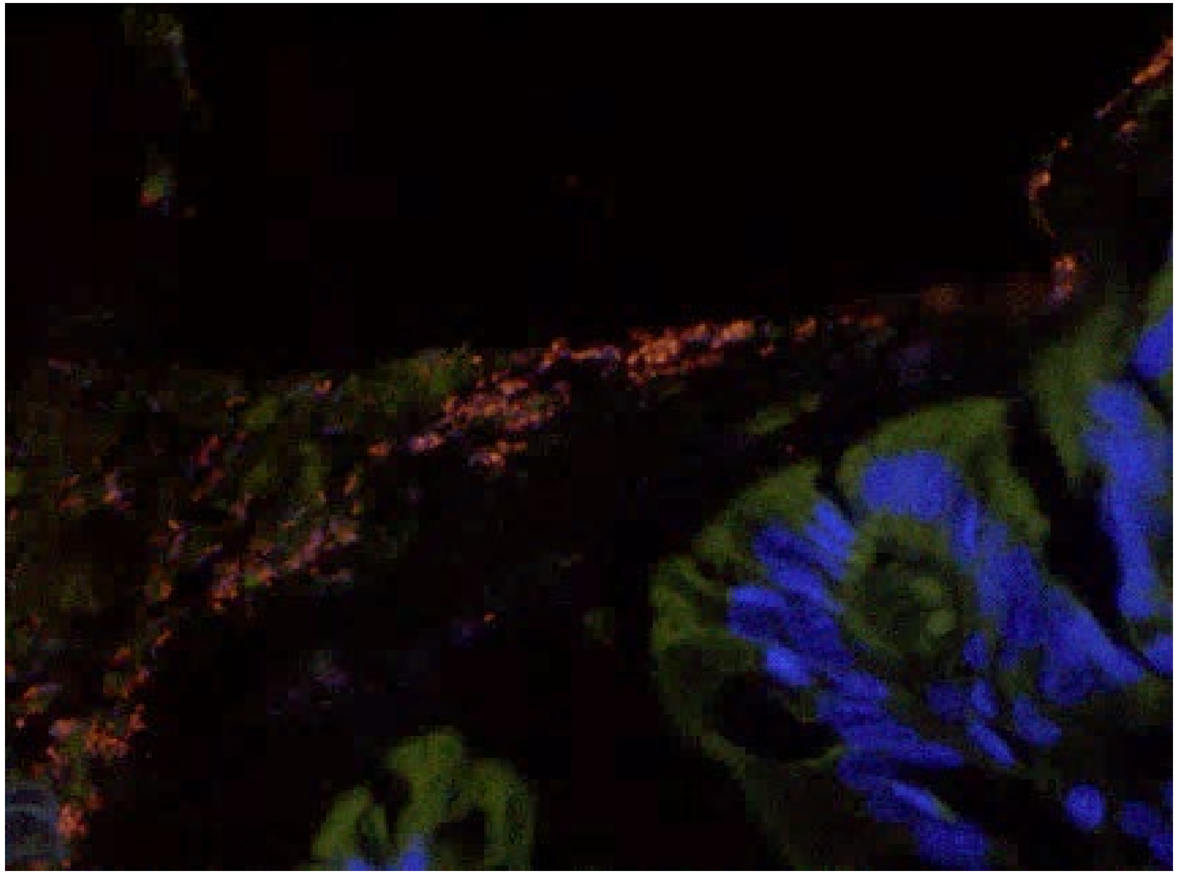
Increased Dysbiosis Index in cats with CE and non-specific clinical signs



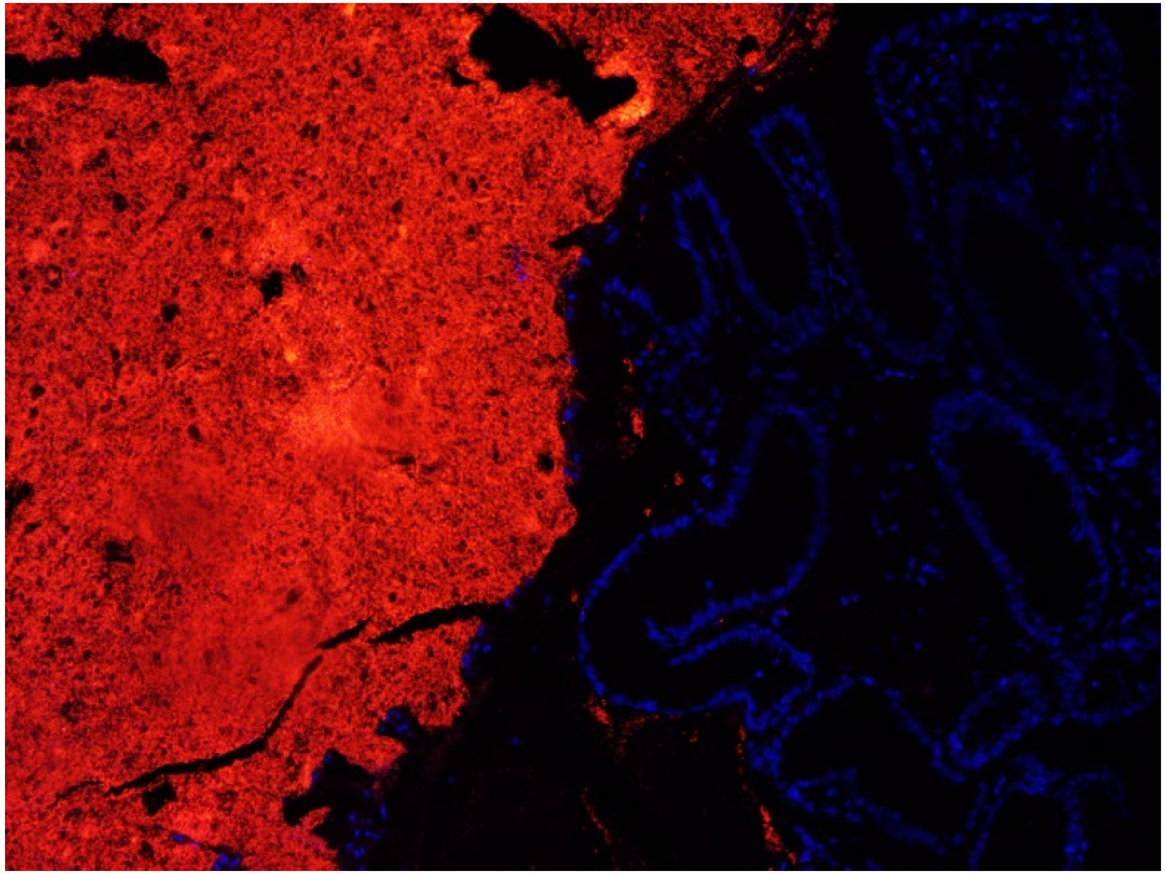


Suchodolski JS, created in Biorender.com

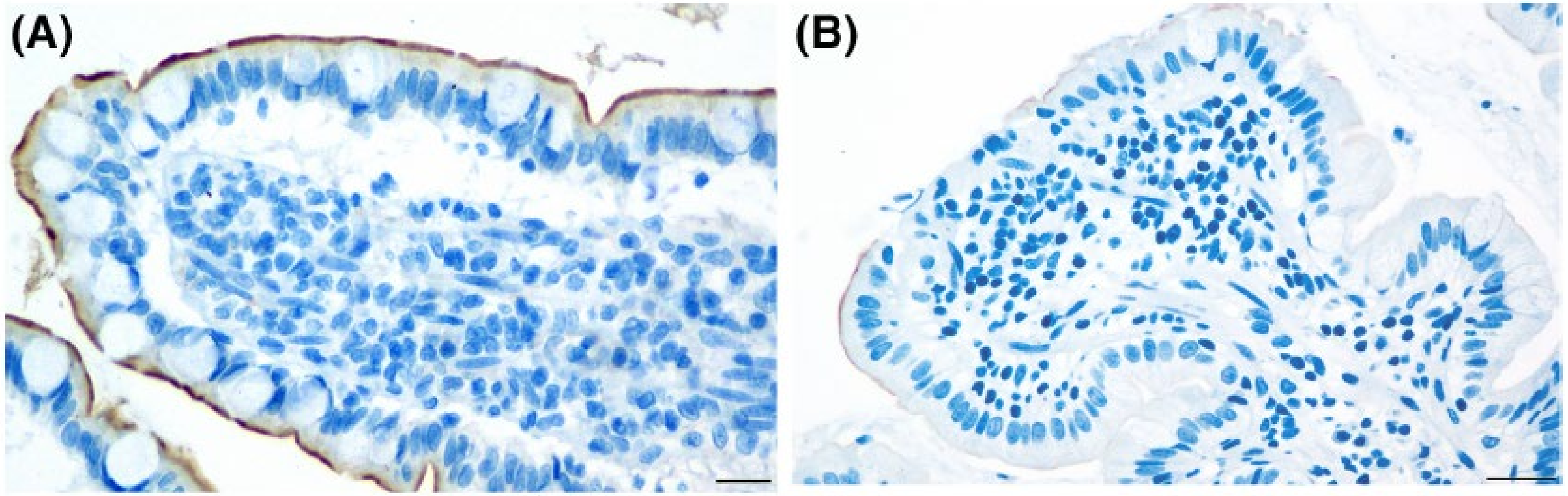
Healthy dog



Dog with chronic enteropathy



MALABSORPTION IN DOGS WITH CE



<u>Bile acid transporter</u> (ASBT) protein in healthy dog (A) and dog with CE(B)

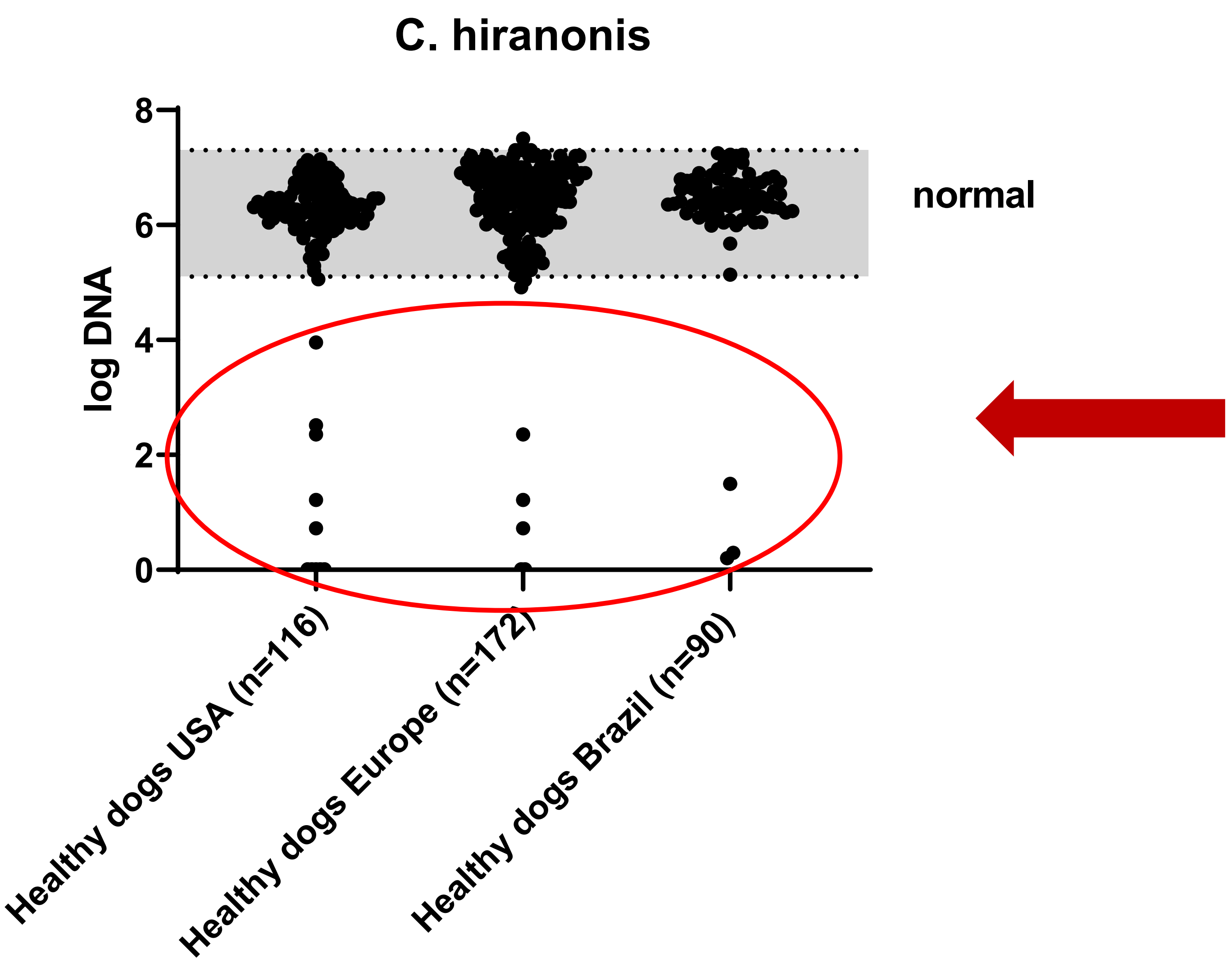
Journal of Veterinary Internal Medicine Open Access ACVIM

Standard Article | Open Access

Comparison of intestinal expression of the apical sodium-dependent bile acid transporter between dogs with and without chronic inflammatory enteropathy

Paula R. Giaretta, Raquel R. Rech, Blake C. Guard, Amanda B. Blake, Anna K. Blick, Jörg M. Steiner, Jonathan A. Lidbury, Audrey K. Cook, Mohsen Hanifeh, Thomas Spillmann, Susanne Kilpinen, Pernilla Syrjä , Jan S. Suchodolski, ... See fewer authors

Abundance of C. hiranonis in fecal samples of healthy dogs



- dogs with <u>decreased</u> abundance of <u>*C. hiranonis*</u> have abnormal bile acid conversion
- increased primary and decreased secondary BA concentration in feces

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RESEARCH ARTICLE

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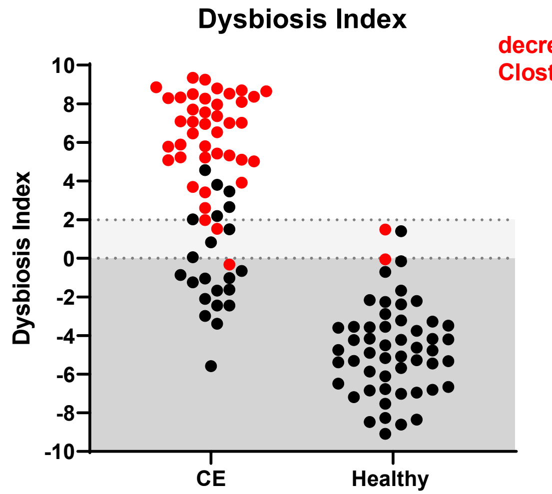
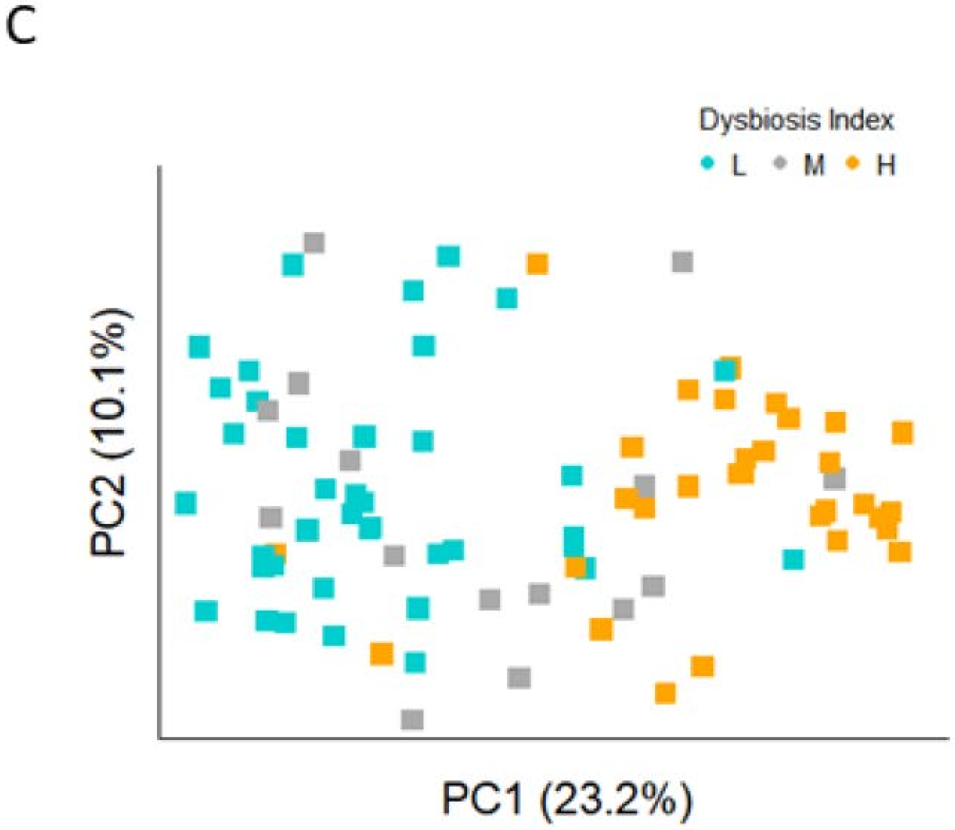
Gut Dysbiosis and Its Associations with Gut Microbiota-Derived Metabolites in Dogs with Myxomatous Mitral Valve Disease

Qinghong Li,[a] Éva Larouche-Lebel,[b] Kerry A. Loughran,[b] Terry P. Huh,[b] Jan S. Suchodolski,[c] Mark A. Oyama[b]

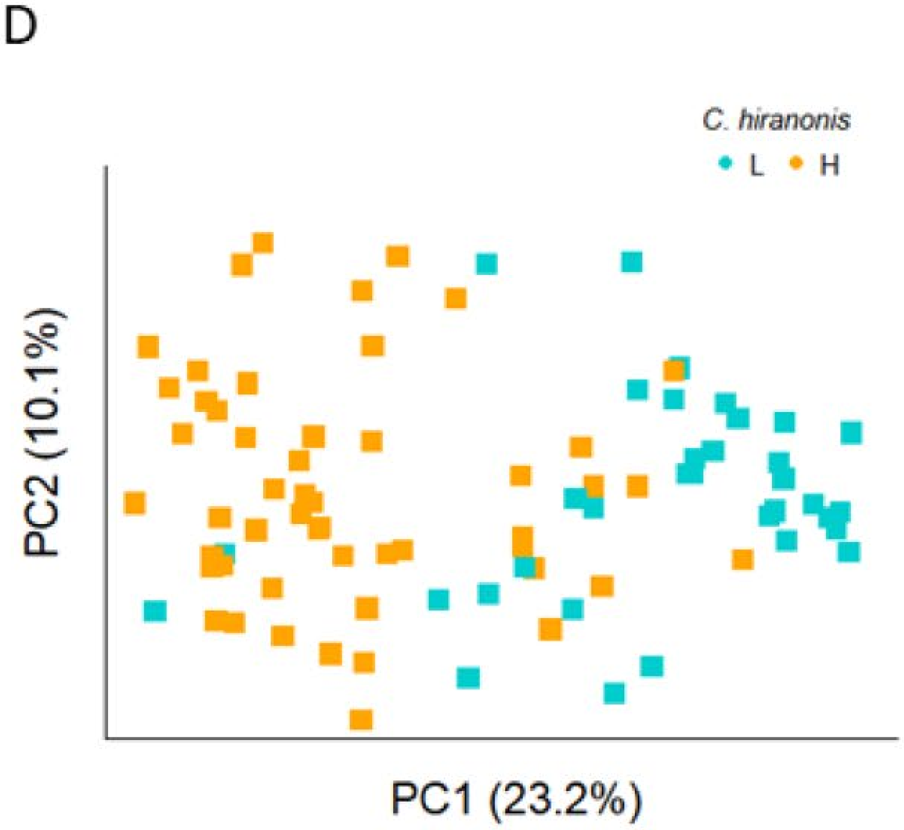


decreased
Clostridium hiranonis

Dysbiosis index



C. hiranonis



PLOS PATHOGENS

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Bile acid-independent protection against *Clostridioides difficile* infection

Andrea Martinez Aguirre, Nazli Yalcinkaya, Qinglong Wu, Alton Swennes, Mary Elizabeth Tessier, Paul Roberts, Fabio Miyajima, Tor Savidge, Joseph A. Sorg

Version 2 Published: October 19, 2021 • https://doi.org/10.1371/journal.ppat.1010015

- bacteria that generate <u>secondary bile acids</u> protect against *C. difficile* disease independently of secondary bile acid generation

- organisms that produce 5-aminovalerate or consume proline / glycine are important

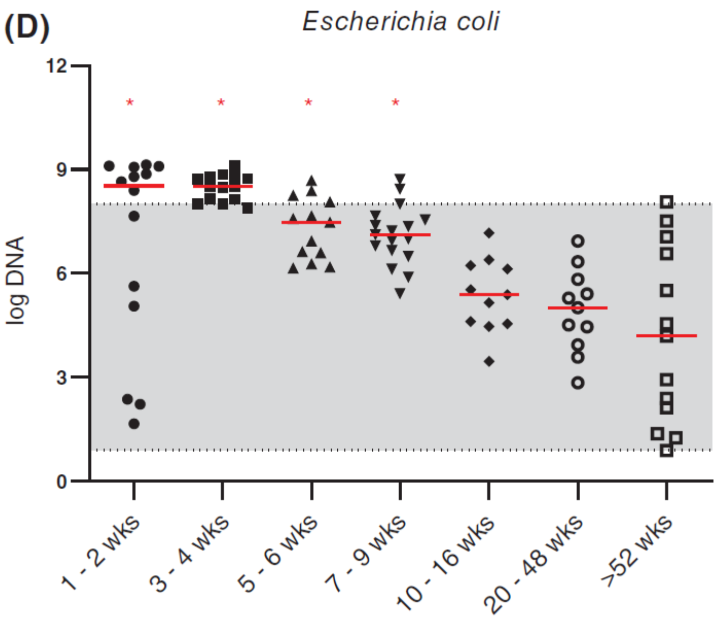
Journal of Veterinary Internal Medicine Open Access ACVIM

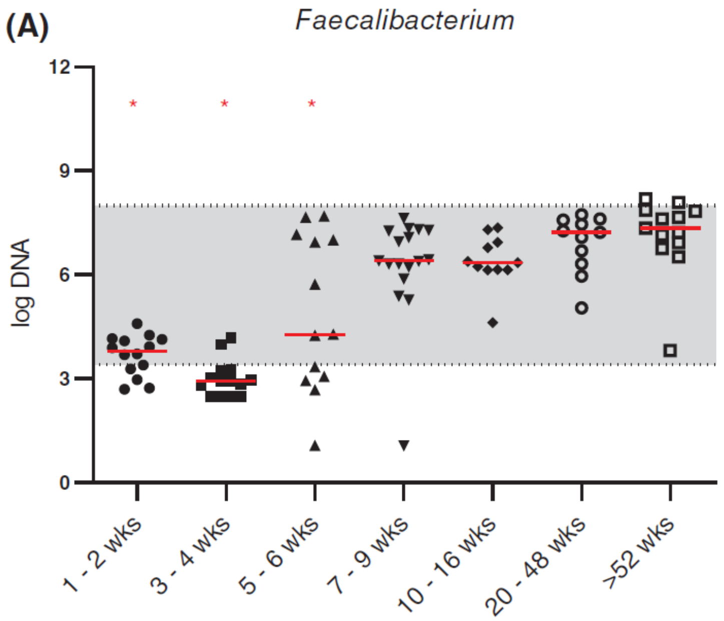
STANDARD ARTICLE | Open Access

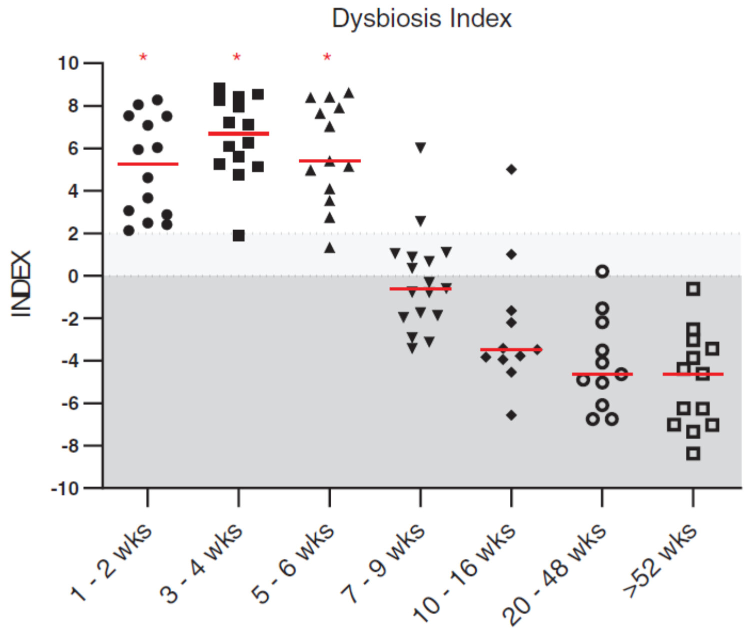
Developmental stages in microbiota, bile acids, and clostridial species in healthy puppies

Amanda B. Blake, Annalis Cigarroa, Hannah L. Klein, Mohammad R. Khattab, Theresa Keating, Patti Van De Coevering, Jonathan A. Lidbury, Jörg M. Steiner, Jan S. Suchodolski,

- puppies are initially colonized by environmental bacteria (eg, E. coli)
- anaerobic normal flora appears around 3-4 months of age

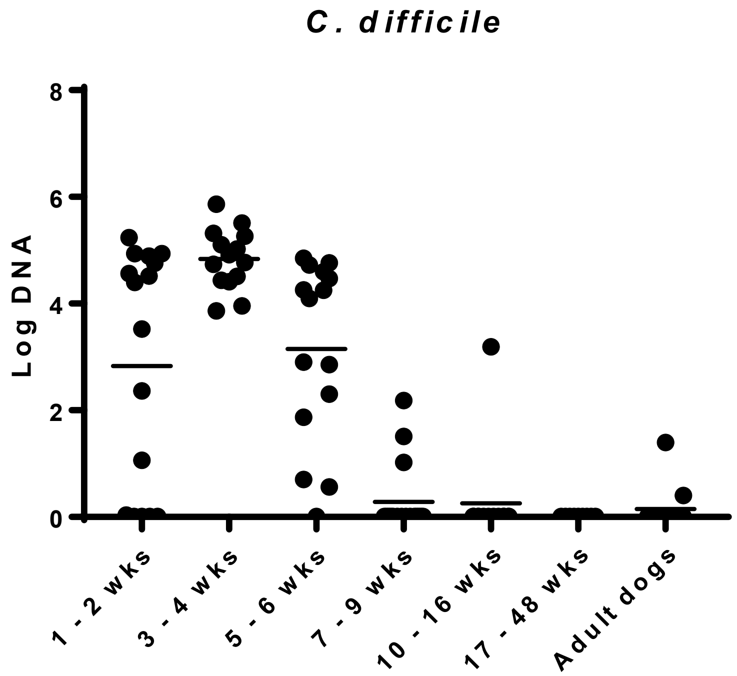


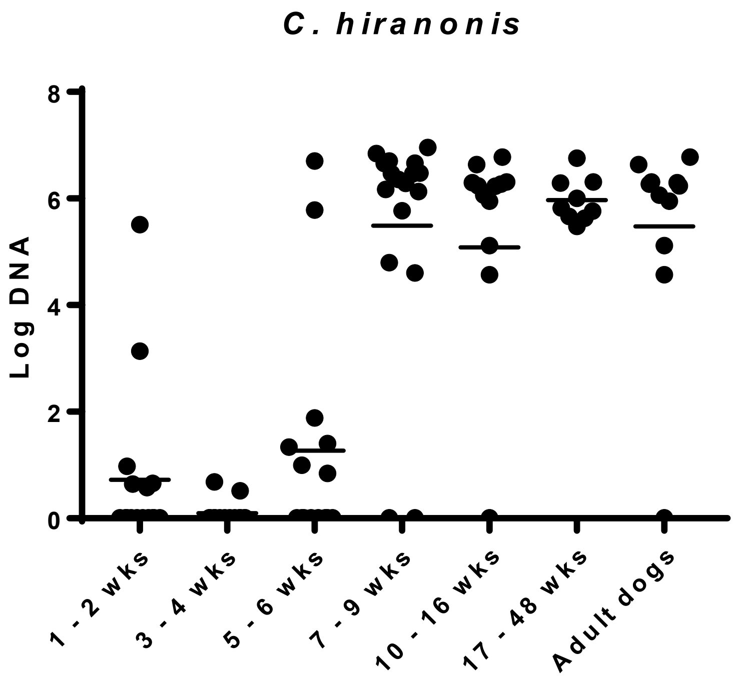


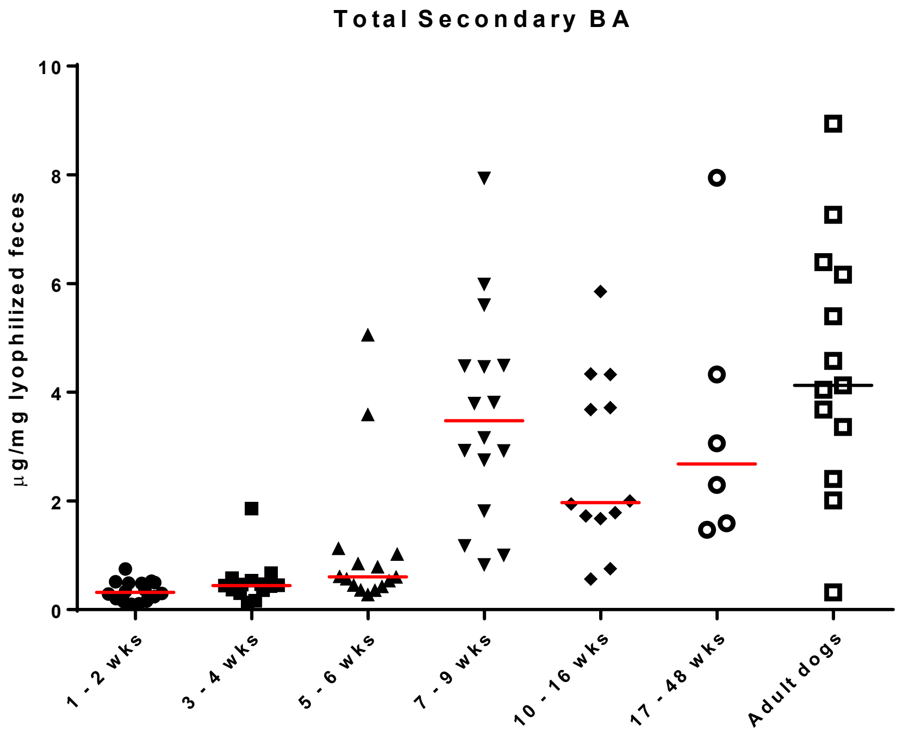


Clostridium hiranonis is important beneficial bacterium in dogs

- converts primary to secondary bile acids (BA)
- correlates with reduction of C. difficile







Journal of Veterinary Internal Medicine Open Access ACVIM

STANDARD ARTICLE | Open Access

Developmental stages in microbiota, bile acids, and clostridial species in healthy puppies

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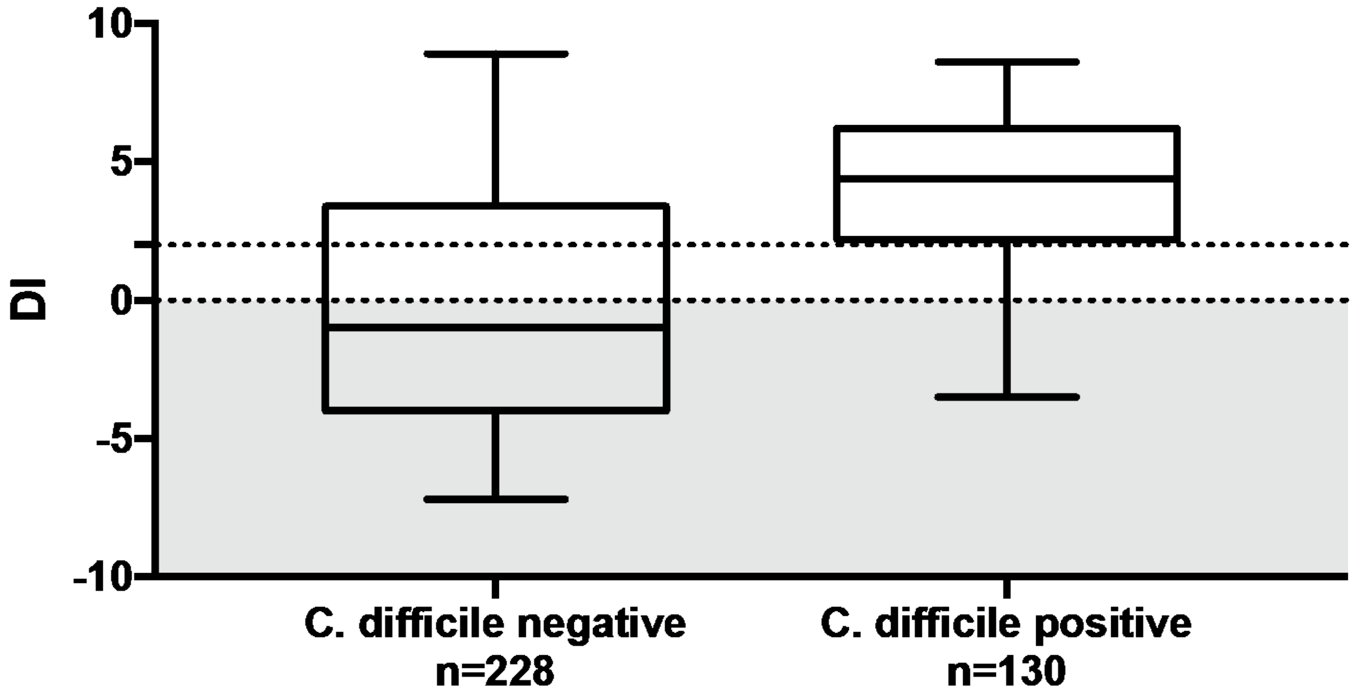
Association between C. diff and Dysbiosis



- dogs positive for C. difficile showed a higher Dysbiosis Index ($p < 0.0001$)
- **<u>115/130 (89%)</u>** of C. difficile positive samples had a DI > 0
- odds ratio of carrying C. difficile 9.5 times higher when DI > 0 than normal DI

abnormal metabolite ratios lead to activation of virulence factors

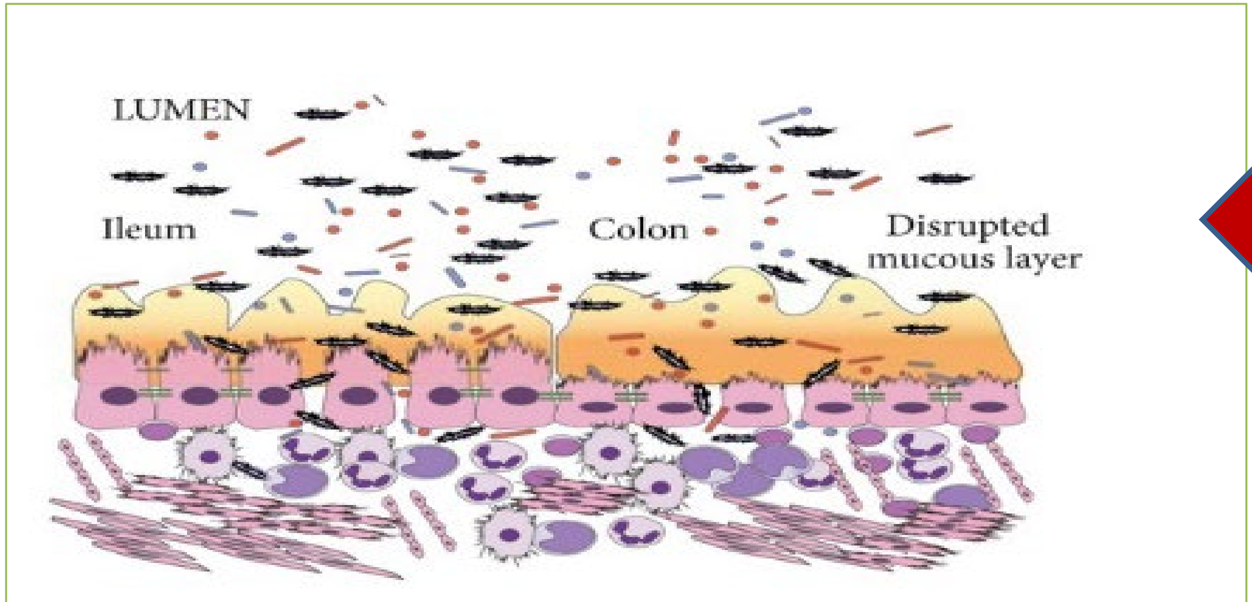
Salmonella, E. coli

abnormal bile acid conversion leads to overgrowth with

C. difficile, C. perfringens, E. coli

Dysbiosis

inflammation, maldigestion, malabsorption



need to identify and treat underlying disorder

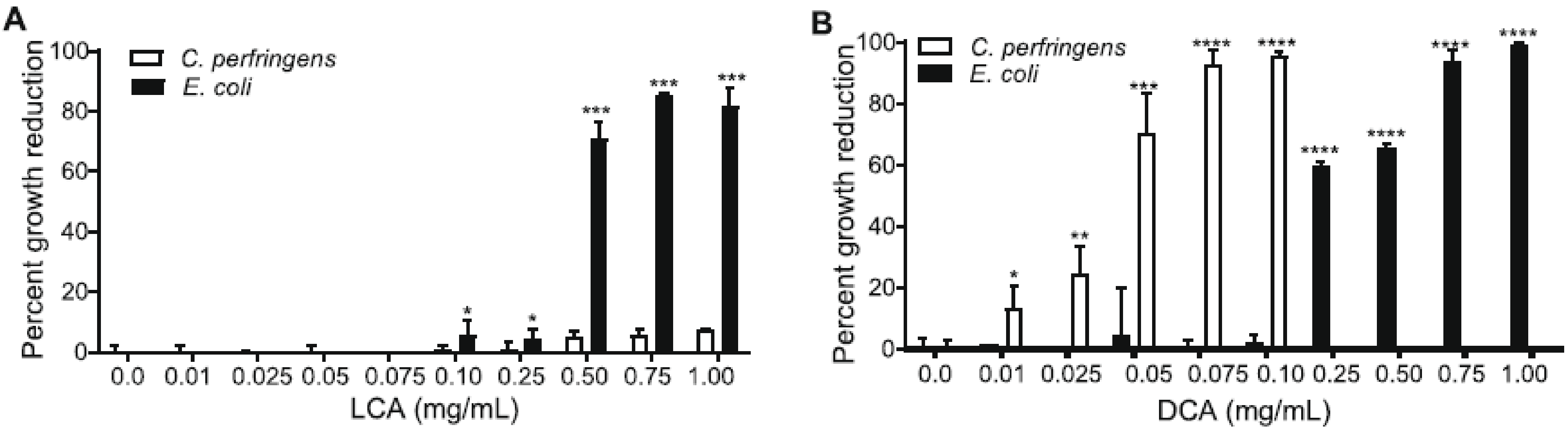
Wang et al. Microbiome (2019) 7:126
https://doi.org/10.1186/s40168-019-0740-4
Microbiome

RESEARCH **Open Access**

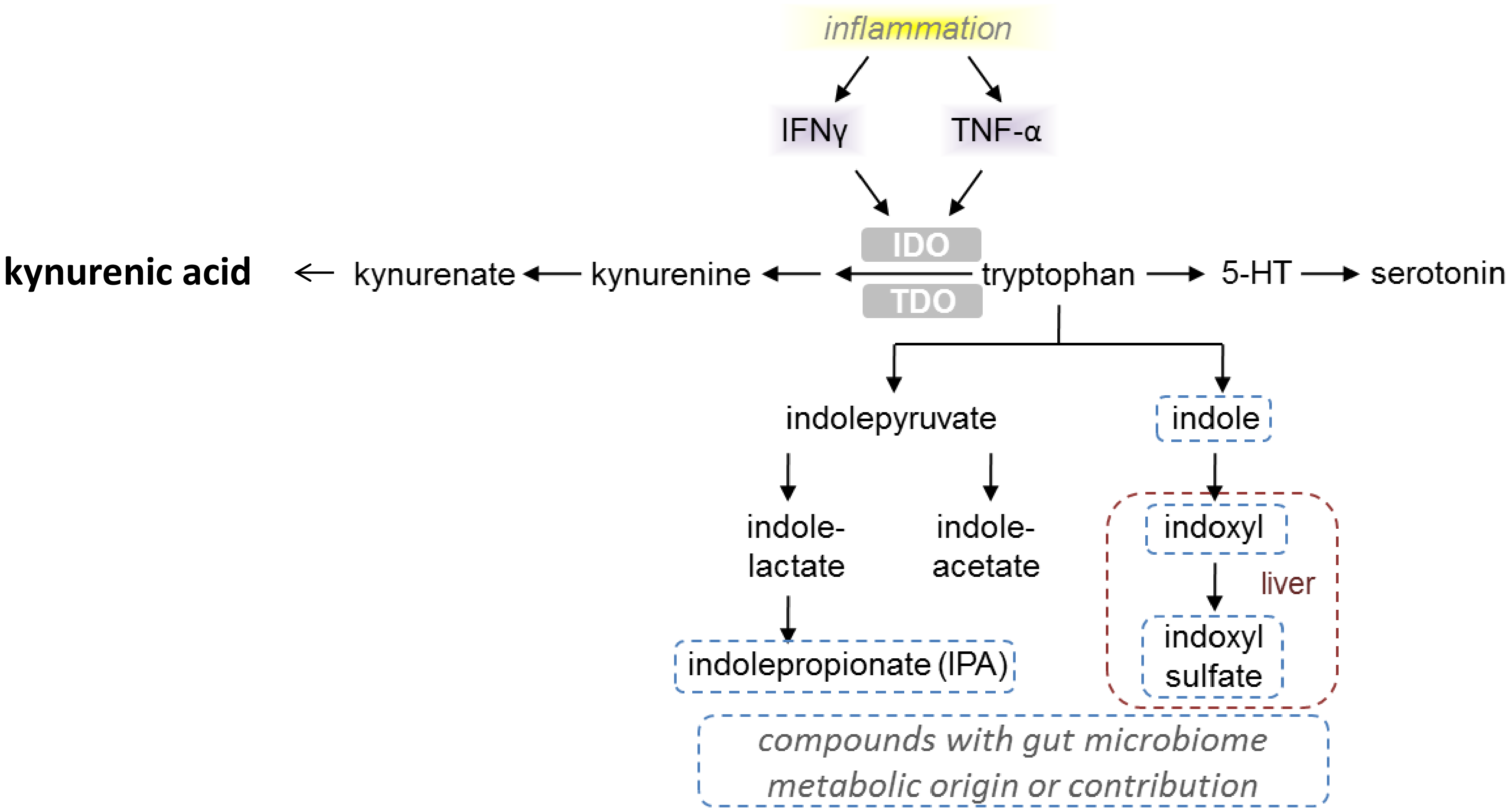
Diet-induced remission in chronic enteropathy is associated with altered microbial community structure and synthesis of secondary bile acids

Shuai Wang[1], Rene Martins[2], Megan C. Sullivan[1], Elliot S. Friedman[3], Ana M. Misic[1], Ayah El-Fahmawi[1], Elaine Cristina Pereira De Martinis[4], Kevin O'Brien[1], Ying Chen[1], Charles Bradley[1], Grace Zhang[1], Alexander S. F. Berry[1,5], Christopher A. Hunter[1], Robert N. Baldassano[5], Mark P. Rondeau[2] and Daniel P. Beiting[1*]

the secondary bile acids lithocholic and deoxycholic acid inhibit the <u>in vitro</u> growth of E. coli and C. perfringens

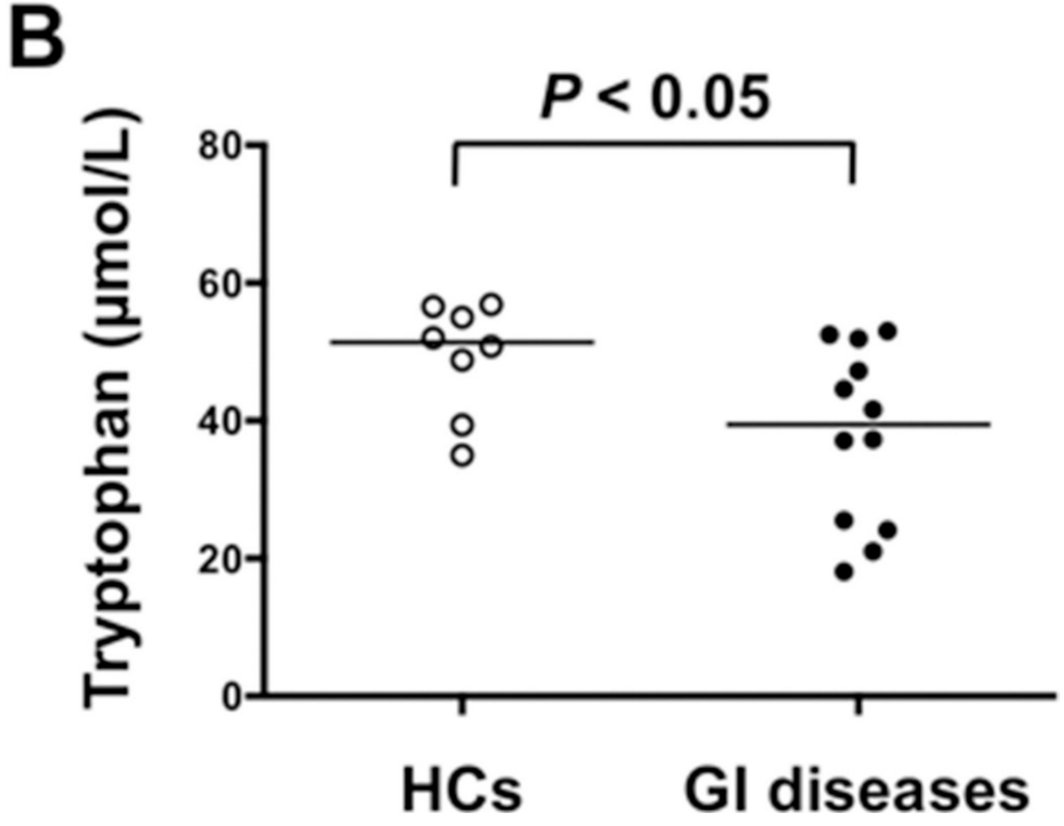


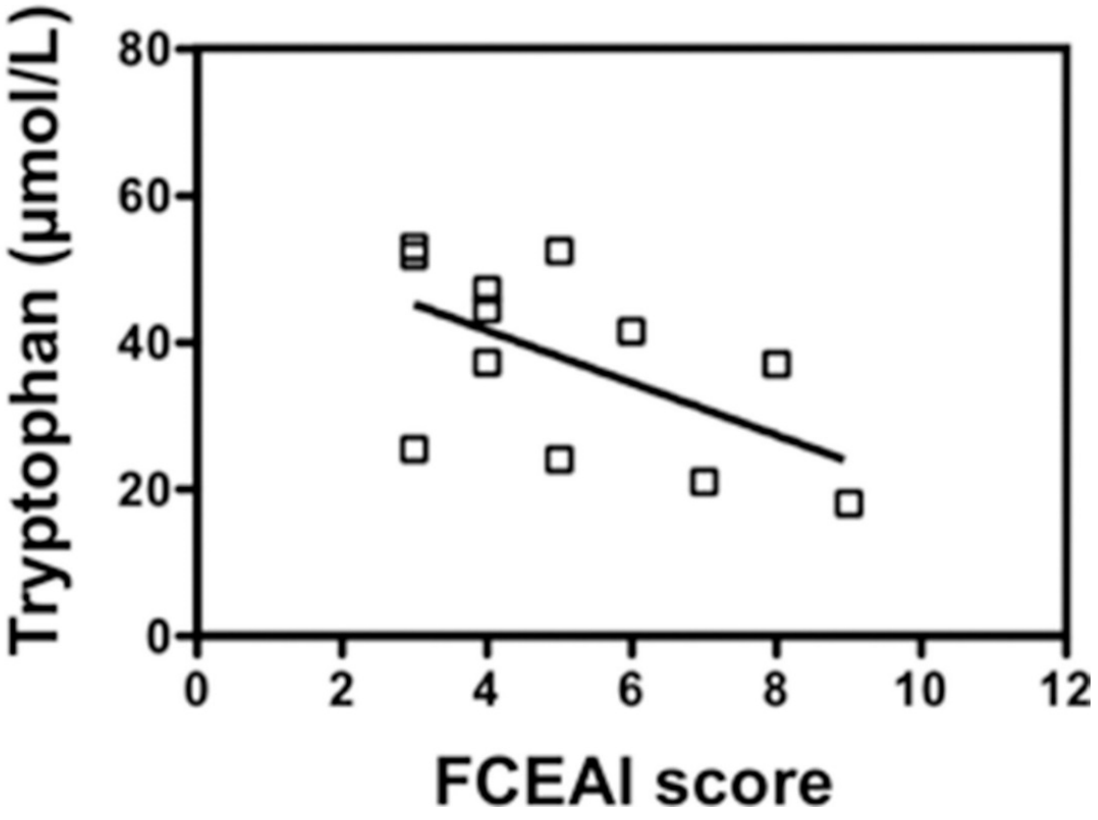
TRYPTOPHAN CATABOLISM IN INFLAMMATION



- Tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO)

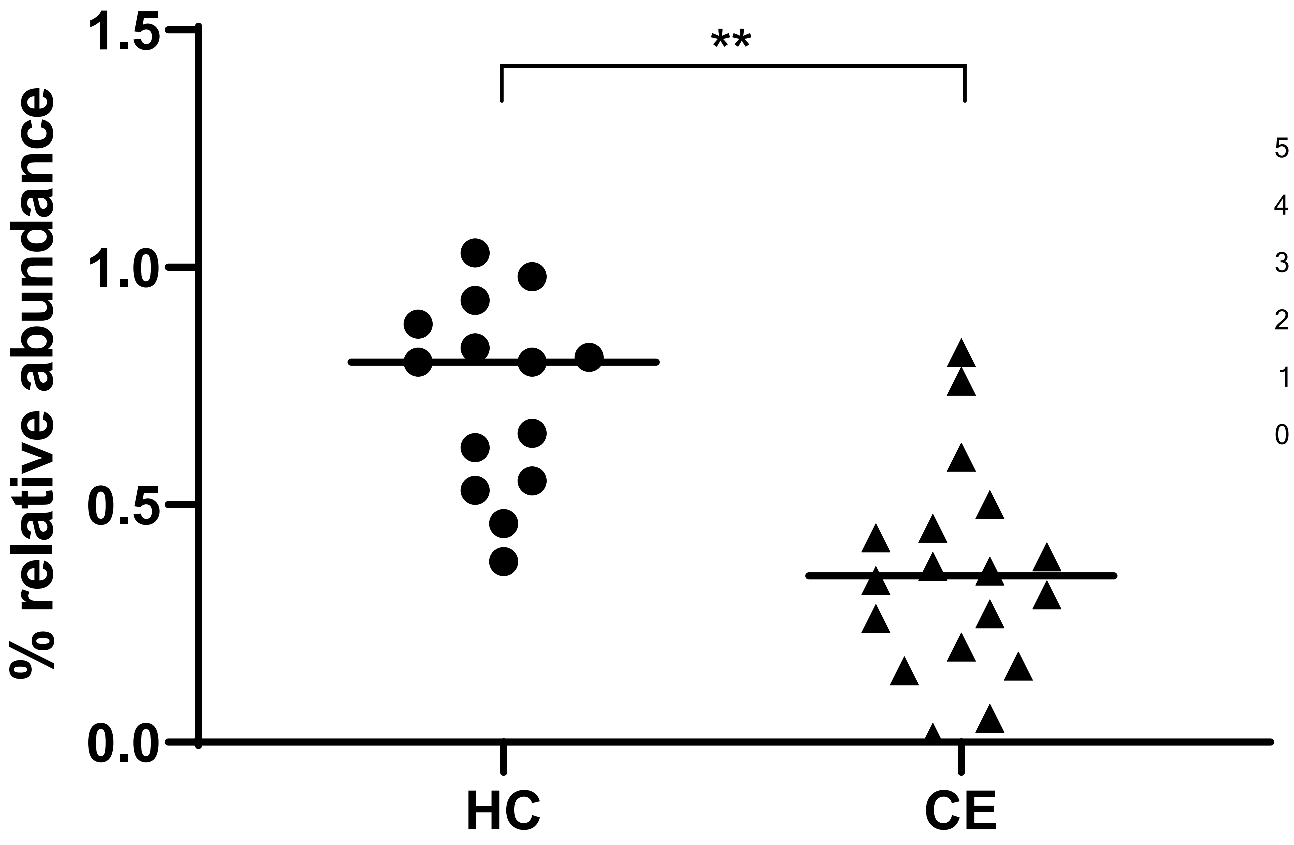
Decreased plasma tryptophan in cats with GI disease



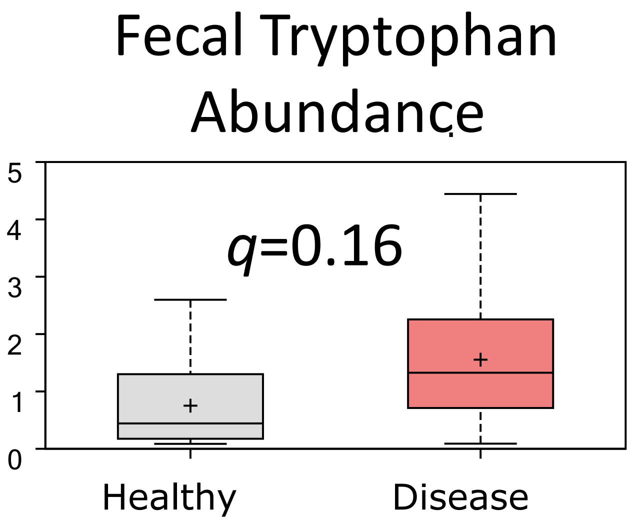


Sakai et. al. *Vet Immunol Immunopathol*. 2017

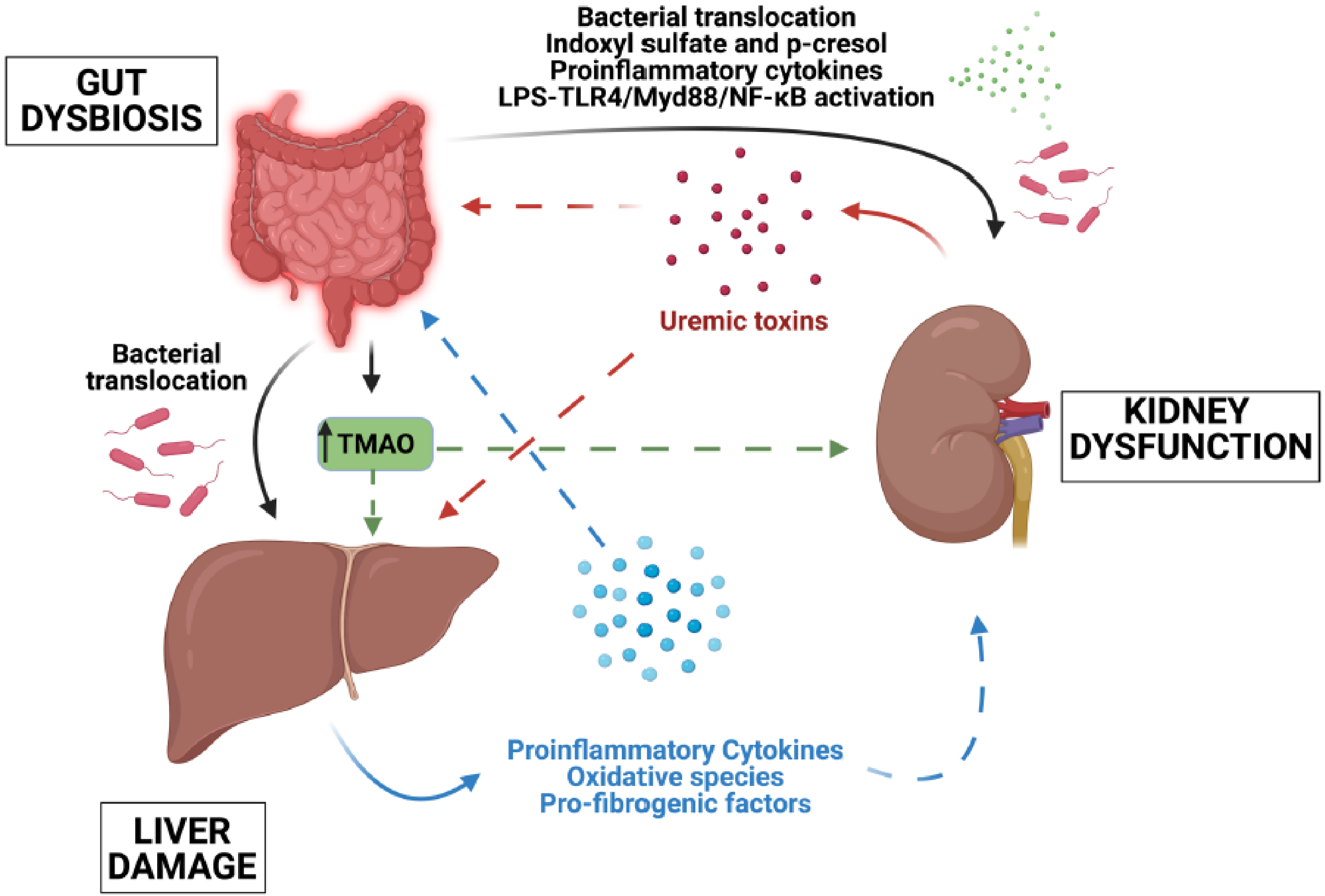
DECREASED BACTERIAL GENE ABUNDANCE FOR TRYPTOPHAN BIOSYNTHESIS IN DOGS WITH CE



Bermudez-Sanchez et. al., ECVIM. 2019



Honneffer et. al., unpublished



Foresto-Neto et al, Renal sensing of bacterial metabolites in the gut-kidney axis. Kidney360 (Am Soc Nephrology) 2021

KIDNEY—GUT AXIS

- bidirectional communication between both organs

- uremia affects GI tract
  - intestinal hypoperfusion, changes in pH, changes in intestinal motility

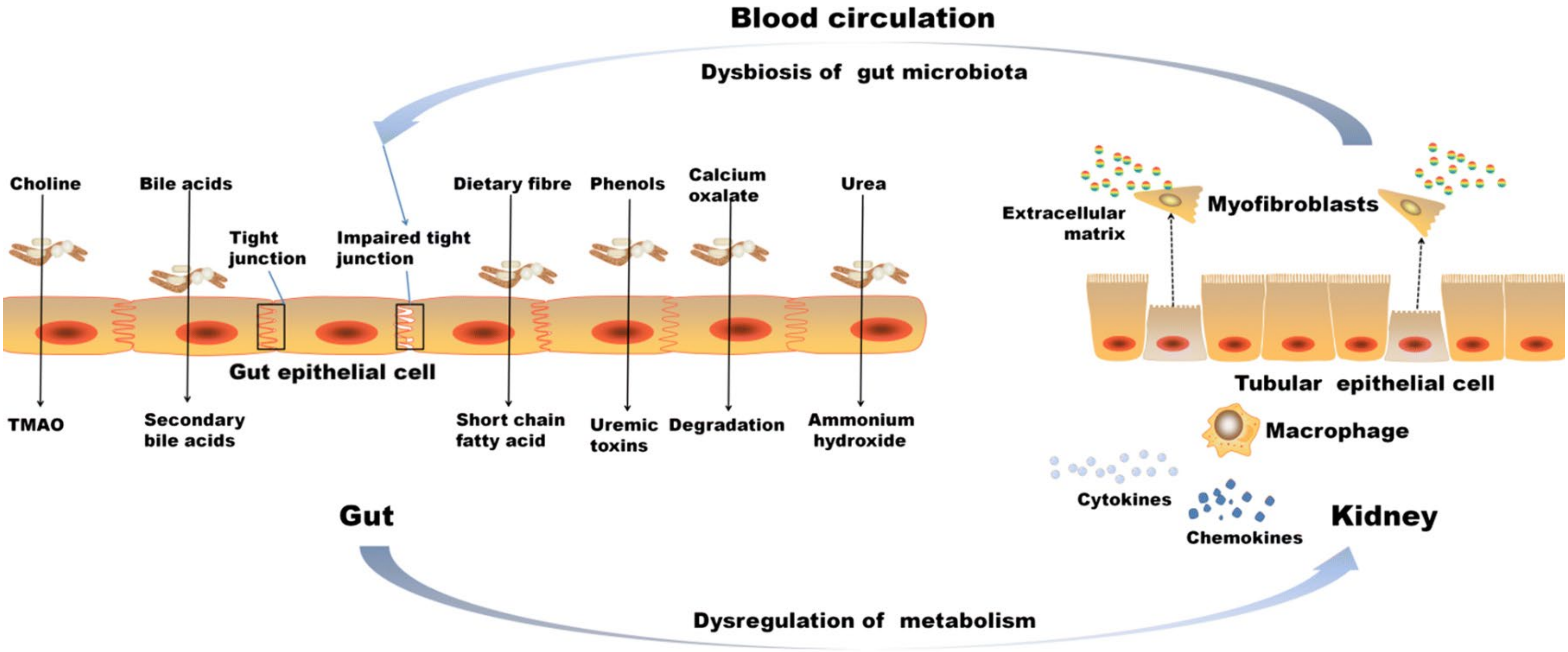
- increased intestinal permeability
  - potential translocation of endotoxin
  - systemic low grade inflammation

KIDNEY—GUT AXIS

- in mouse models environmental changes cause intestinal microbiota dysbiosis
  - low fiber intake
  - drugs (e.g., antibiotics, phosphate binders)

- increased systemic uremic toxins may also cause intestinal dysbiosis

- dysbiosis together with increased intestinal permeability
  - potentiates endotoxemia and low-grade systemic inflammation
  - which in turn may affect the progression of CKD



Bidirectional pathway

Microbiome–metabolome reveals the contribution of gut–kidney axis on kidney disease

Yuan-Yuan Chen †, Dan-Qian Chen †, Lin Chen, Jing-Ru Liu, Nosratola D. Vaziri, Yan Guo and Ying-Yong Zhao

Journal Translational Medicine 2019

OPEN ACCESS

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ELSEVIER

Veterinary Clinics of North America: Small Animal Practice

Volume 51, Issue 1, January 2021, Pages 155-169

Impact of Changes in Gastrointestinal Microbiota in Canine and Feline Digestive Diseases

Anna-Lena Ziese Dr med vet [a], Jan S. Suchodolski Dr med vet, PhD [b]

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https://tx.ag/DysbiosisGI