Fecal Lipid Metabolites are Correlated with Intestinal Permeability and Serum Concentrations of Microbial Tryptophan Metabolites in Dogs with Exocrine Pancreatic Insufficiency

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Introduction

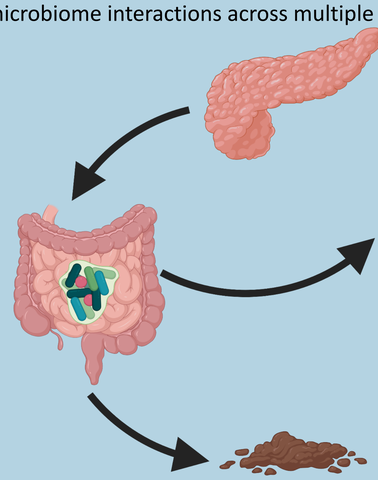
Exocrine Pancreatic Insufficiency (EPI) is a malabsorptive syndrome caused by insufficient secretion of pancreatic digestive enzymes. Failure to digest dietary proteins, lipids, and carbohydrates causes malabsorptive diarrhea, enteric microbiota dysbiosis, vitamin deficiencies (B12, E, A), and cachexia. The most common cause of EPI in dogs is pancreatic acinar atrophy (PAA). EPI is treated with oral pancreatic enzyme supplementation, however 40% of dogs with EPI have a sub-optimal clinical response to enzyme therapy.

In dogs, EPI is diagnosed when the concentration of serum canine trypsin-like immunoreactivity (cTLI) is less than 2.5 µg/L. Previous studies have shown that dogs with cTLI in an equivocal range (2.6-5.6 µg/L) have PAA, a state termed subclinical EPI (sEPI), that often progresses to EPI.

EPI is associated with enteric microbiota dysbiosis which is known to cause mucosal abnormalities, including increased intestinal permeability, in dogs and other mammals. Altered microbial metabolism and mucosal barrier dysfunction could contribute to the persistence of clinical signs in some dogs with EPI after enzyme replacement therapy. The goal of this study was to evaluate host-microbiome metabolic interactions in dogs with EPI treated with pancreatic enzymes, and to determine if altered microbial metabolites in serum or feces are associated with increased intestinal permeability.

Methods

We collected serum and fecal samples from 20 dogs with EPI, 5 dogs with sEPI, and 10 healthy controls. We used a systems-biology approach to detect host-microbiome interactions across multiple biologic scales:



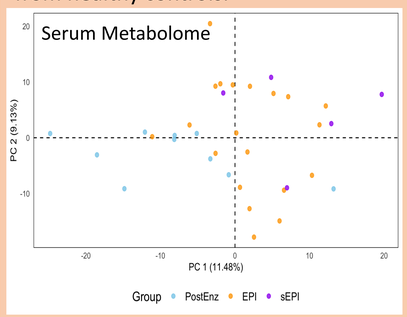
Serum metabolome:
759 biochemicals by HPLC-MS/MS

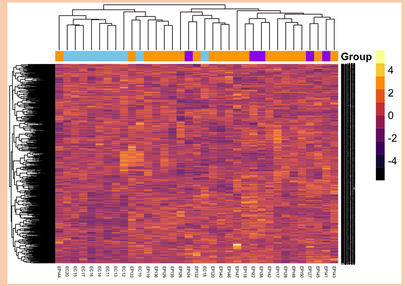
Intestinal Permeability:
Fecal Zonulin by ELISA

Fecal Lipid Metabolites:
fatty acids and bile acids by GCMS

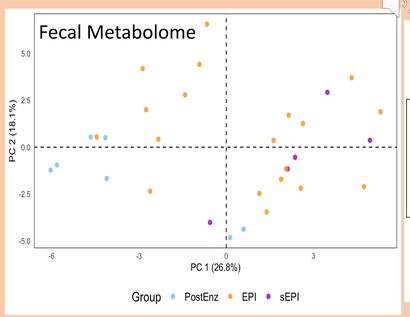
Results

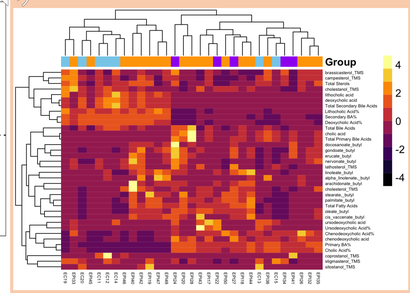
759 Biochemicals were detected in the serum samples. Principal component analysis (PCA) separates the serum metabolomes of dogs with EPI and sEPI from healthy controls.



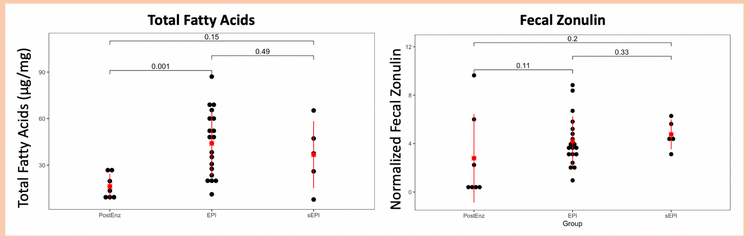


38 lipid metabolites were quantified in the fecal samples. Principal component analysis (PCA) separates the fecal metabolomes of dogs with EPI and sEPI from healthy controls.





Dogs with EPI and sEPI have increased fecal concentrations of fatty acids and zonulin.



26 microbial metabolites were detected the serum dogs' sera. Of these, microbial metabolites of dietary tryptophan were inversely correlated with fecal zonulin

Biochemical	Pearson's	P-Value
Indolepropionate	-0.44	0.016
Indolelactate	-0.35	0.047

Results

Fecal bile acids are correlated with fecal concentrations of zonulin

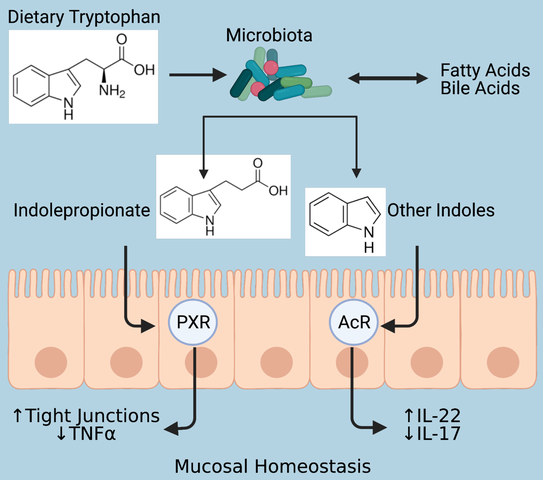
Correlated Variables		Pearson's	P-Value
Total fecal primary bile acids	Fecal zonulin	0.44	0.012
Total fecal secondary bile acids	Fecal zonulin	-0.63	0.0001

Fecal secondary bile acids are correlated with fecal serum concentrations of indolepropionate

Correlated Variables		Pearson's	P-Value
Total Secondary Bile Acids	Serum indolepropionate	0.54	0.001

Conclusions

We have documented numerous significant associations among serum microbial metabolites and changes in the fecal metabolome and intestinal permeability in dogs with EPI. Microbial metabolites of tryptophan were associated with intestinal permeability. Previous studies have revealed a significant role for indoles, microbial metabolites of tryptophan, in the regulation of enteric mucosal homeostasis.



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