DIET-INDEPENDENT CORRELATIONS BETWEEN NAFLD DEVELOPMENT AND GUT MICROBIOTA IN MUCOSAL AND LUMINAL COMPARTMENTS OF THE ILEUM AND COLON IN LDLR-/-.LEIDEN MICE

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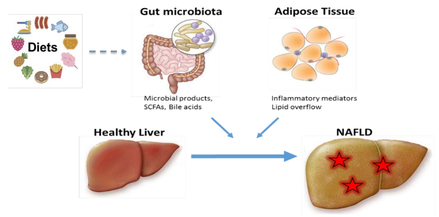
Background

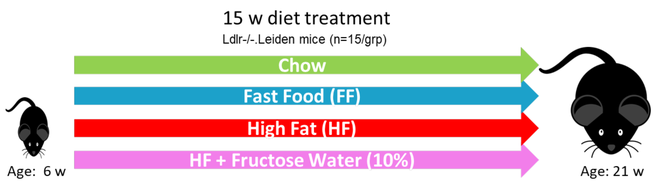
Development of non-alcoholic fatty liver disease (NAFLD) has been linked to the homeostasis of other organs such as white adipose tissue (WAT) and the gut (microbiota composition, gut permeability), which in part can be modulated by diet. Since bacterial colonization differs along the gastrointestinal tract *and* differences in composition between the mucosal and the fecal microbiota may be expected, it is unclear whether microbiota changes in specific compartments of the ileum and colon may be more closely linked to host health than the conventionally-studied fecal microbiota.



Aim

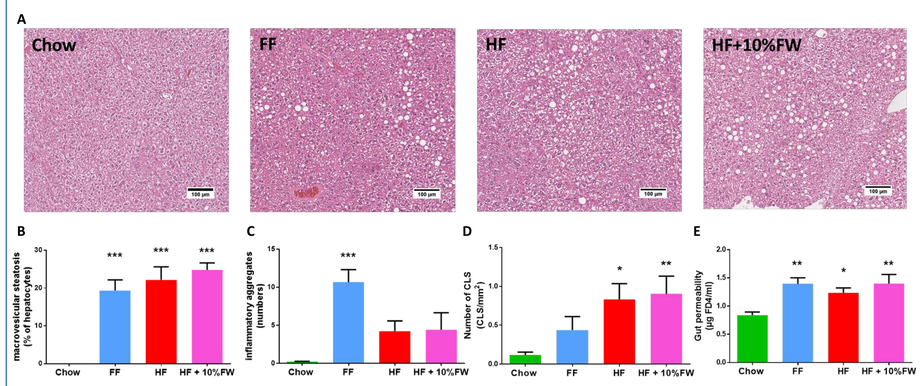
To perform a systematic microbiota analysis in ileum and colon in both the fecal and mucosal compartment to investigate whether there are diet-independent changes in gut microbial compartments that correlate with obesity and NAFLD endpoints.

Methods



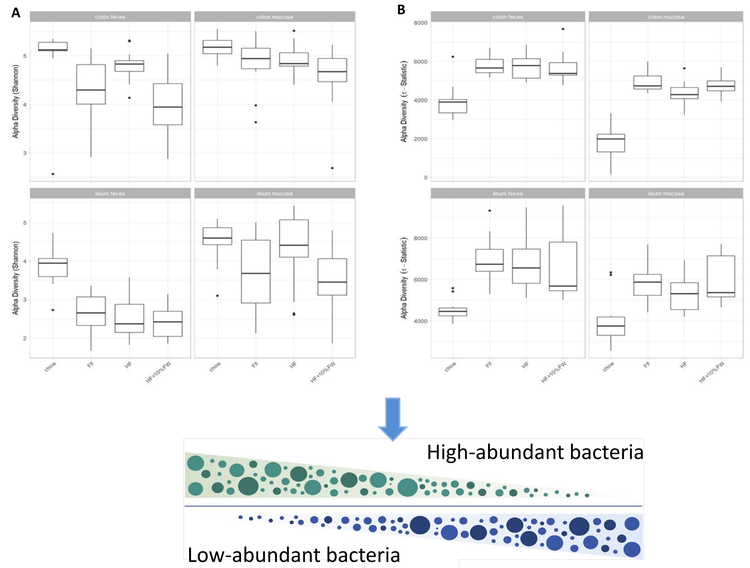
	Chow	FF	HF	HF+10%FW
Fat	9%En/3.3%w.w	41%En/20%w.w Butter fat	45%En/24%w.w Lard	Same as HF
Protein	24%En/19%w.w	14%En/18%w.w Casein	20%En/24%w.w Casein	Same as HF
Carbohydrate	67%En/40.8%w.w	44%En/49%w.w Fructose	35%En/41%w.w Sucrose	Same as HF
Cholesterol	-	-	-	-
Energy/gram	3.2 kcal/g	4.5 kcal/g	4.7 kcal/g	Same as HF
Fiber	4.9%w.w	5.1% w.w	5.8% w.w	Same as HF
Drink	Water	Water	Water	10% w.v Fructose

All energy-dense diets induce NAFLD, WAT inflammation and increase gut permeability



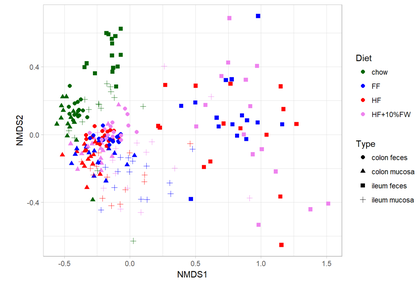
*(**A**) Representative images of HE-stained liver sections (**B**) quantification of macrovesicular steatosis and (**C**) lobular inflammation [number of inflammatory aggregates]. (**D**) White adipose tissue inflammation [number of crown-like structures (CLS)]. (**E**) Functional gut permeability analysis (FD4 test). *p≤0.05 or **p≤0.01 or ***p≤0.001*

Energy-dense diets differentially affect microbiota diversity in high-abundant and low-abundant bacteria



*Microbiota alpha diversity was analyzed with the (**A**) Shannon index (sensitive for high-abundant bacteria) and (**B**) the tail statistic (sensitive for low-abundant bacteria)*

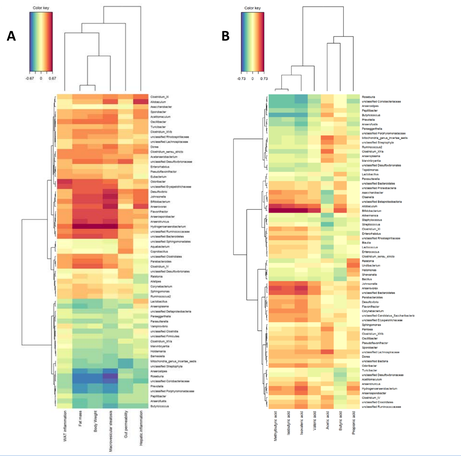
Microbiome composition of energy-dense diet groups overlap and differ from chow



Community profiles were analyzed on genus level, compared by Bray-Curtis dissimilarity and visualized in a non-metric multidimensional scaling (NMDS) plot.

Diet-independent correlations exist between microbiota and disease endpoints: added value of mucosal compartment

		Histological & functional readouts	Metabolites
Colon	Feces	0.56	0.43
	Mucosa	0.71	0.62
Ileum	Feces	0.60	0.62
	Mucosa	0.52	0.41



*Correlation analysis between the microbiota-composition and (**A**) histological and functional readouts of NAFLD or (**B**) plasma levels of gut-derived metabolites were performed with regularized canonical correlation analysis (rCCA analysis).*

Conclusions

- Low abundant bacteria increase in diversity and high abundant bacteria decrease in diversity upon energy dense-diet feeding in all compartments
- Mucosal microbiota composition is consistently more stable than the fecal compartment in terms of diversity
- Diet-independent correlations exist between certain bacteria and disease endpoints
- Correlations are strongest for colon mucosa

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