Changes in the gut microbiota and fermentation products associated with enhanced longevity in acarbose-treated mice.

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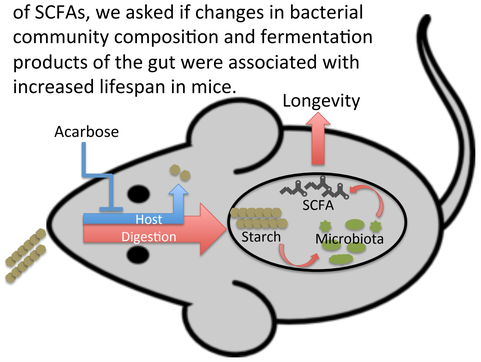
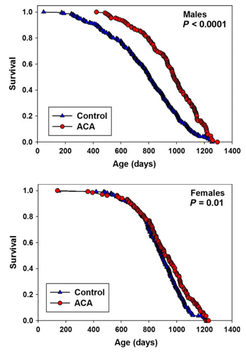
Introduction

Mice treated with acarbose (ACA) continuously during adulthood, have a median lifespan approximately 20% and 5% longer in males and females, respectively [1]. By inhibiting the enzymes that normally degrade starch, ACA increases the quantity of polysaccharide entering the colon [2] leading to increased production of short-chain fatty acids (SCFAs) by bacteria [3]. Given the documented benefits of SCFAs, we asked if changes in bacterial community composition and fermentation products of the gut were associated with increased lifespan in mice.

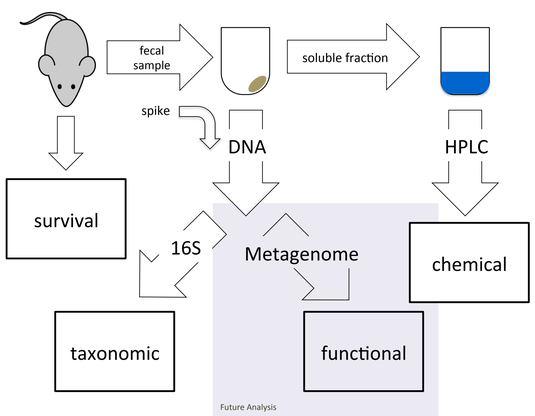




Methods

At three sites, The University of Michigan (UM), University of Texas San Antonio Health Science Center (UT), and The Jackson Labs (TJL), mice were either fed a control diet, or the same diet amended with 1000 ppm ACA from 8 months of age onwards. Individual fecal samples were collected from mice between 762 and 973 days of age. At each site, samples from 24 control and 24 ACA treated mice were collected, with an equal number from males and females. Matched longevity data were collected for sampled mice from UM and UT.

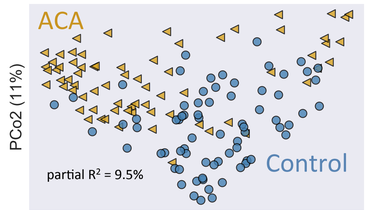
Metabolite measurements (HPLC) and bacterial community surveys (16S) were carried out on fecal samples. Samples were spiked with a constant quantity of *Sphingopyxis alaskensis* stationary phase culture before DNA extraction, enabling comparison of rRNA gene densities across samples [4]. Operational taxonomic units (OTUs) were defined at a 97% similarity threshold.

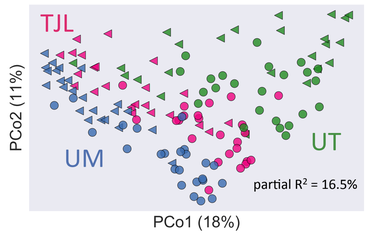


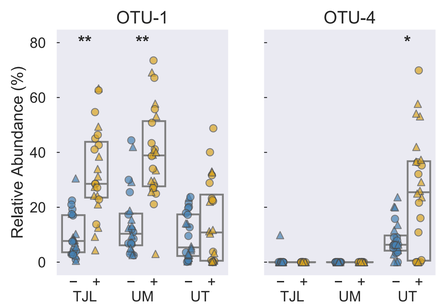
Results

Surveys of the 16S rRNA gene confirm that ACA modulates the composition of the fecal bacterial community. A principle coordinate analysis based on Bray-Curtis dissimilarities (**figure right**) demonstrates the significant separation between control and treated mice while controlling for site and sex ($p < 0.001$). Communities at each site were also distinct ($p < 0.001$).

The difference between treatment groups was dominated by large increases in the relative abundance of two OTUs, designated OTU-1 and OTU-4 (**figure below**). The spike-adjusted abundance of the 16S rRNA gene from these taxa was greater in ACA. Both OTUs are classified as members of the largely uncultured family S24-7 in order *Bacteroidales*, which has previously been observed to be common in the gut of mice and to respond to dietary perturbations [5].

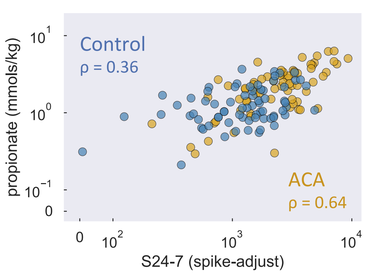


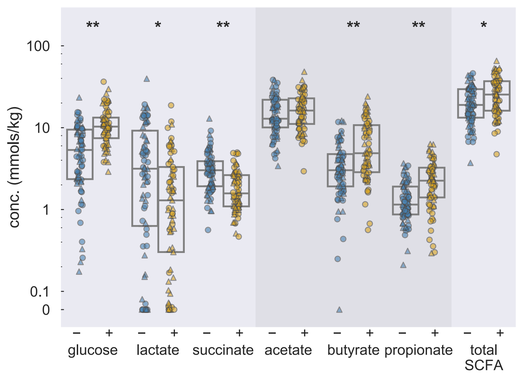




Along with shifts in bacterial populations, concomitant changes were observed in the metabolic profile, in particular increased SCFAs (**figure right**). Propionate was found to be subject to an interaction between sex and treatment, resulting in a greater increase in propionate with ACA treatment in males than in females.

Propionate was correlated with the abundance of S24-7 in both control and treated mice ($p < 0.05$ for both).
The **figure below** plots the spike-adjusted abundance of 16S rRNA genes from OTUs classified as family S24-7 against the concentration of propionate. Reconstructed genomes have suggested that propionate production is common in members of the S24-7 family [5].





Including concentrations of acetate, butyrate, and propionate in a Cox proportional hazards model, while controlling for treatment, site, and sex (**table below**) resulted in a substantially better fit to the data (ΔAIC = -3.5). Butyrate and propionate were associated with increased survival and acetate with reduced survival.

covariate	log HR (standardized)	P > |t|
propionate	-0.39	0.012
butyrate	-0.54	0.030
acetate	0.46	0.041

Conclusions

- Fecal metabolite profiles in mice treated with ACA were shifted towards **increased butyrate and propionate** concentrations, SCFAs linked with decreased inflammation and host health.
- Bacterial communities responded with **large changes in composition**, particularly favoring two OTUs in family S24-7. The 16S rRNA density of this family was **associated with higher propionate concentrations**.
- Fecal **propionate, butyrate, and acetate** concentrations were statistically significant **predictors of mouse longevity** while controlling for treatment.
- **Future work** is needed to (1) test a causal role for SCFAs in host longevity, (2) explain the high variability between samples, (3) and understand the dramatic increases in OTU-1 and OTU-4.

Citations

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Acknowledgments & Contact

This work was supported by NIA grant AG022303, a Burroughs Wellcome Fund training grant, and the Glenn Foundation for Medical Research.

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