Maastricht University | Maastricht UMC+

Faculty of Health, Medicine and Life Sciences

NUTRIM

School of Nutrition and Translational Research in Metabolism

NIMOlab Nutrition Integrative Metabolism & Obesity

Putative players in metabolic health: Gut-bacteria derived membrane vesicles have distinct immunogenicity dictated by bacterial producer strain

Jari Verbunt [1,2], Johan Jocken [2], Emanuel E. Canfora [2], Ellen Blaak [2], Paul Savelkoul [1,3] and Frank Stassen [1]

1 Department of Medical Microbiology, infectious diseases & Infection prevention, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center+, 6229 ER Maastricht, The Netherlands
2 Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center+, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands
3 Department of Medical Microbiology and Infection Control, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Introduction

The microbiota play a pivotal role in human health, as in metabolic diseases the composition of the gut microbiota is often altered. Gut-bacteria produce bacterial membrane vesicles (bMVs) containing bacterial cargo, and in animal models, gut-bMVs exit the intestine to reach host organs. Here they can affect energy metabolism leading to diabetic phenotypes. We relate the gut-bMV repertoire to the bacterial composition in 12 participants with prediabetes (BMI > 25 kg/m2) and 12 healthy controls. Lastly, we characterize immunogenicity of these bMVs in vitro to relate taxa to properties.

Objective

To analyse bacterial membrane vesicle composition and to characterize their immunogenicity using in vitro models

Methods

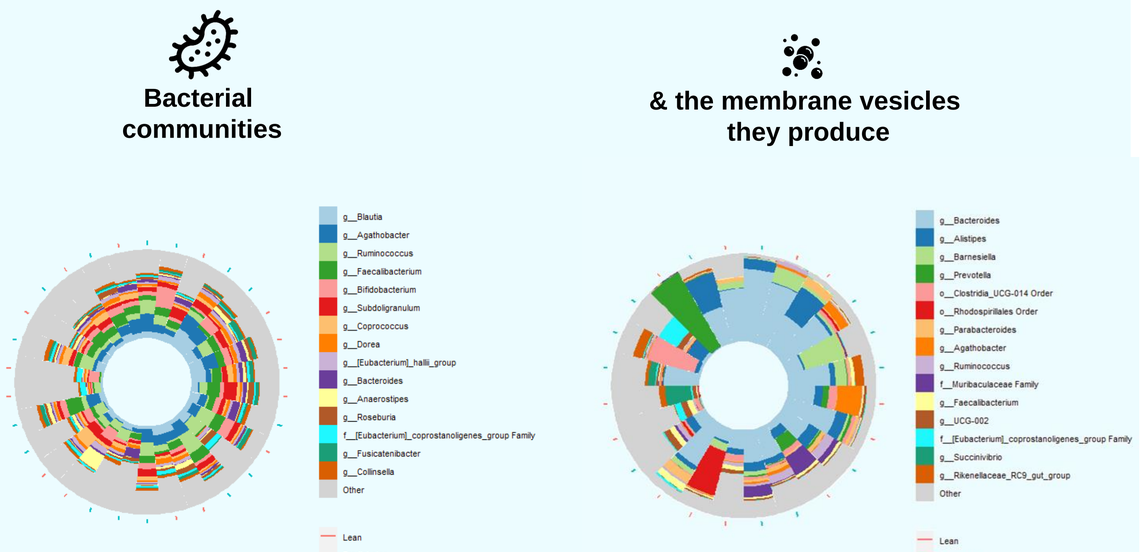
bMVs were purified from faeces through (ultra)centrifugation and size exclusion chromatography. DNA was obtained from bacteria and bMVs and subjected to 16S rRNA variable region amplification and Illumina sequencing. Faeces-derived bMVs were incubated with human THP-1 macrophages and adipocytes. Cytokine expression and secretion (IL6, TNFα, IL1β) was related to vesicle composition.

	BMI <25 (n=12)	*BMI ≥25 (n=12)*	*p*
	Mean (SD)	*Mean (SD)*	
BMI (kg/m^2)	*23.9 (1)*	*30.09 (2.5)*	*<0.001*
Age (yrs)	*53.7 (12)*	*59.3 (6.5)*	*0.21*
weight (kg)	*76.8 (6.4)*	*97.3 (9.6)*	*<0.001*
length (cm)	*179 (5.9)*	*180 (6.3)*	*0.85*
WH_ratio	*0.92 (0.04)*	*1.01 (0.05)*	*<0.001*
Fasting gluc (mM)	*5.0 (0.3)*	*6.1 (0.7)*	*<0.01*
2h gluc OGTT (mM)	*4.1 (1.2)*	*8.3 (2.6)*	*<0.001*

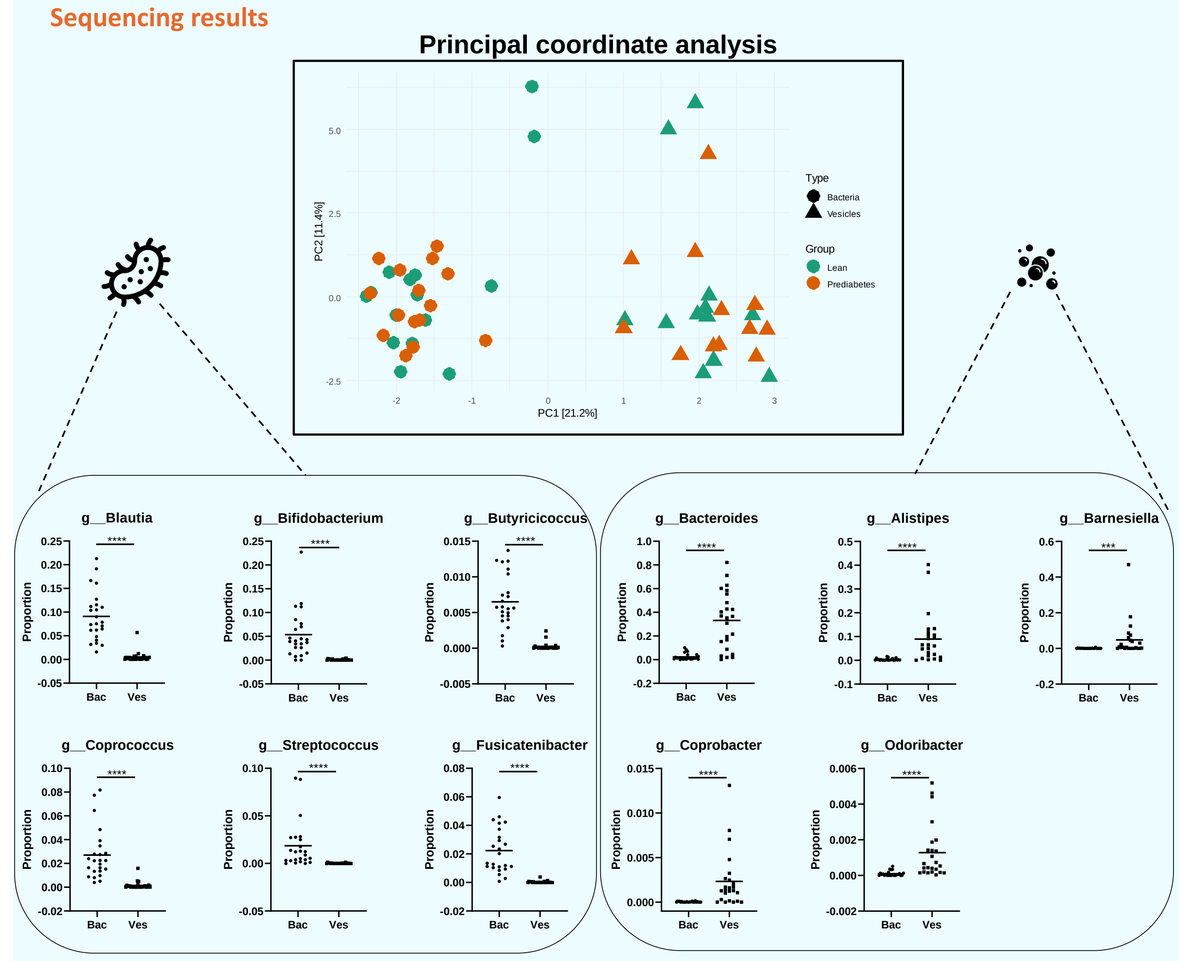
Table 1. Baseline study population characteristics. Fecal samples originated from previous work investigating effect of dietary fibres on colonic fermentation [4]. Only morning samples taken at baseline were used in this presented work. Unpaired t-test used for significance testing.

Results

Per gram of faeces, ~10^{11} bMVs were isolated. Bacterial and bMV composition are dissimilar in terms of bacterial DNA content



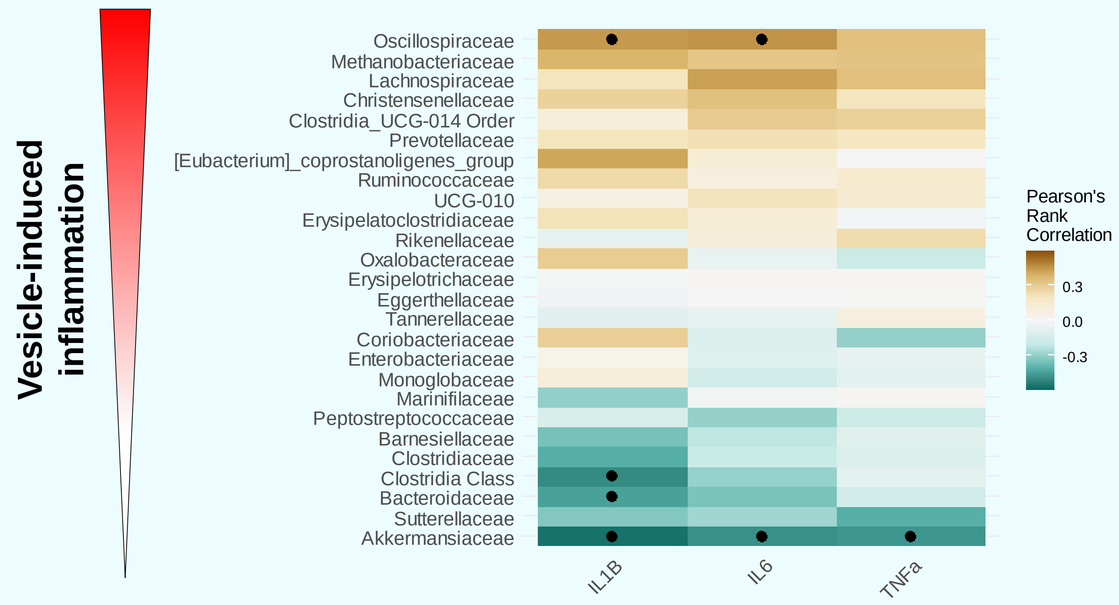
Sequencing results



- **No compositional differences observed between distinct metabolic phenotypic groups**
- Gram positive taxa dominate bacterial compositions
- Gram negative taxa dominate vesicle compositions

Stimulation results

In vitro immunogenicity of bMVs in vitro is largely explained by abundance of vesicle DNA belonging to Oscillospiraceae and Lachnospiraceae (proinflammatory), whilst a higher proportion of Akkermansiaceae vesicles correlates with lesser vesicle-induced inflammation



Discussion/conclusions

- Gut-derived bMVs add complexity to microbiome-host interactions as their composition is different from the composition of the bacteria that produced them.
- Compositions are not different between studied groups, but bMV immunogenicity is dictated by origin.
- Research into translocation of gut-bMVs to human organs is warranted in order to investigate effects on host metabolism.

References

1.Jovel J, Dieleman LA, Kao D, Mason AL, Wine E. The human gut microbiome in health and disease. Metagenomics. 2018:197-213
2.Amabebe E, Robert FO, Agbalalah T, Orubu ES. Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. British Journal of Nutrition. 2020;123(10):1127-37.
3.Kameli N, Borman R, López-Iglesias C, Savelkoul P, Stassen FR. Characterization of feces-derived bacterial membrane vesicles and the impact of their origin on the inflammatory response. Frontiers in cellular and infection microbiology. 2021;11:667987.
4.Canfora EE, Hermes GD, Müller M, Bastings J, Vaughan EE, van Den Berg MA, et al. Fiber mixture-specific effect on distal colonic fermentation and metabolic health in lean but not in prediabetic men. Gut microbes. 2022;14(1):2009297.

Correspondence to:
Jari Verbunt

Jari.verbunt@maastrichtuniversity.nl
https://www.nimolab.nl/
www.linkedin.com/in/jariverbunt

Dept of : Department of Medical Microbiology, infectious diseases & Infection prevention
Dept of : Human Biology

T + 31 4338 77341

Maastricht University
Maastricht University Medical Centre
P.O. Box 616, 6202 AZ Maastricht
P. Debyelaan 25, 6229 HX Maastricht