Production of deoxycholic acid by low-abundant microbial species is associated with impaired glucose metabolism

Annie Wahlström, Ariel Brumbaugh, Wilhelm Sjöland, Lisa Olsson, Hao Wu, Marcus Henricsson, Annika Lundqvist, Kassem Makki, Stanley L. Hazen, Göran Bergström, Hanns-Ulrich Marschall, Michael A. Fischbach & Fredrik Bäckhed

INTRODUCTION

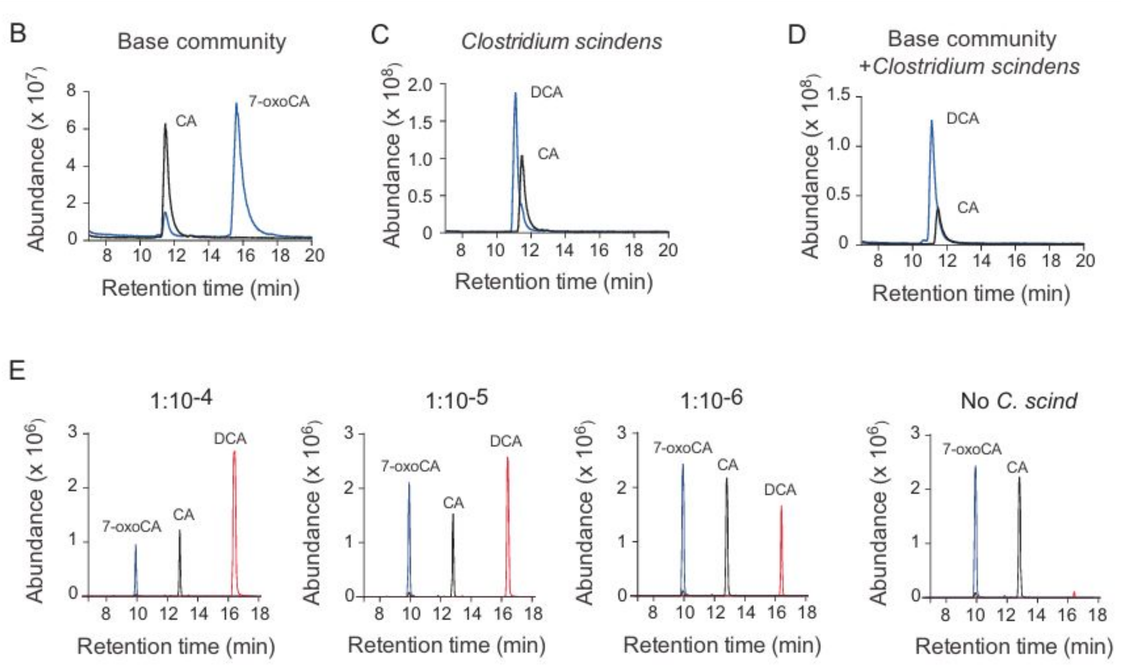
With the growing burden of cardiometabolic diseases such as diabetes mellitus (DM) on public health worldwide[1], there is an ever-growing need for therapeutic modalities that overcome the challenges faced by today's treatment methods. One potential avenue we can use to achieve this goal is by utilising the human gut microbiota. There is a strong association between DM and the gut microbiota[2,3], with some studies suggesting that gut microbial metabolites play a key role in mediating glucose tolerance and dysbiosis[4]. Many papers currently link DM to changes in gut microbiota composition[5,6]. While many studies link DM to changes in gut microbiota composition, these changes may not fully capture the complexity of the in vivo relationship. Therefore, this study aims to support the hypothesis that low abundance species, that do not significantly impact the overall gut microbiota composition, have the ability to produce a significant change in metabolite output which, in turn, plays a crucial role in the development of DM and other cardiometabolic diseases.

METHODS

- Synthetic community strains were cultured in pre reduced Mega Medium or EG agar at 37 °C in an anaerobic chamber.
- Germ-free female C57Bl/6 mice were maintained in flexible plastic gnotobiotic isolators under a strict 12h light cycle under standard conditions, and fed an autoclaved chow diet.
- For human studies, 200 individuals were recruited from two clinical cohorts in Sweden, with both cohorts comprising men and women aged 50-64.
- Total DNA from mouse caecal contents and bacterial culture pellets were extracted using the PowerFecal DNA Isolation kit and quantified using Qubit Ds DNA BR assay kit.
- Bile acid profiling was done by GC-MS, UPLC, Q-TOF-MS and UPLC-MS/MS.

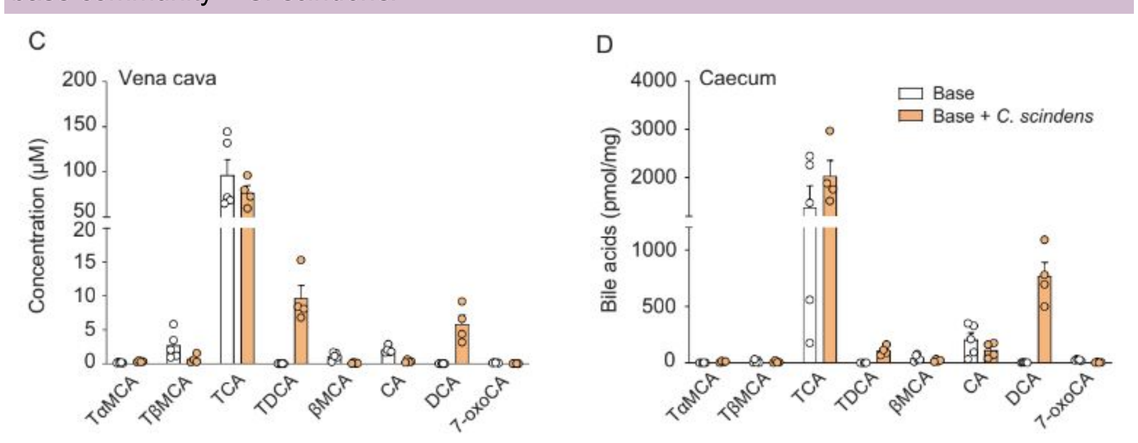
RESULTS

Fig 1. In vitro assessment of DCA formation by bacterial species included in the simplified communities.



B: Base community members (*Bacteroides caccae*, *Bacteroides vulgatus*, *Eubacterium rectale*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Parabacteroides distasonis*, *Bacteroides ovatus*, *Ruminococcus torques* and *Dorea longicatena*) cultured together
C: *Clostridium scindens* cultured individually
D: Base community + *C. scindens* cultured together
E: Assessment of DCA production after 24h in serial dilutions of *C. scindens* in the base community, spiked with CA

Fig 2. Bile acid levels in vena cava and caecum of mice colonized with base community or base community + *C. scindens.*

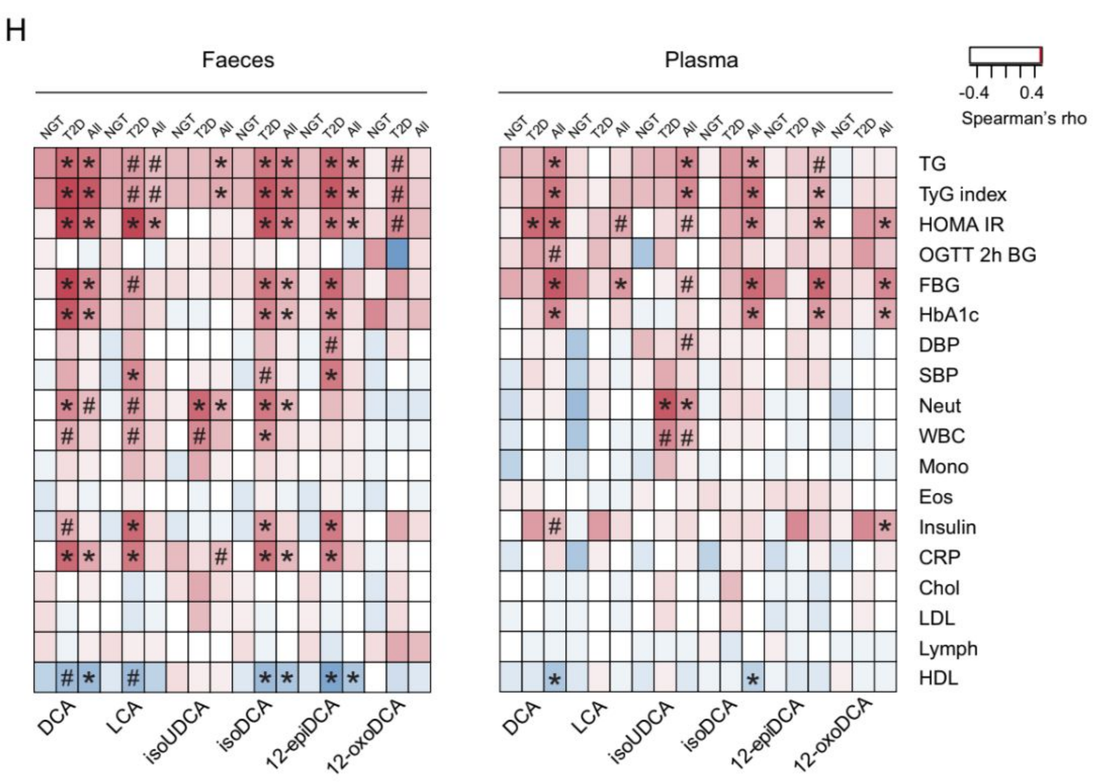


C: Bile acid levels in vena cava of mice colonized with base community or base community + C. scindens.
D: Bile acid levels in caecum of mice colonized with base community or base community + C. scindens.

CONCLUSION

The bacterial species *C. scindens* contributes to DCA production which in turn will negatively impact glucose metabolism in T2DM patients, possibly resulting in cardiometabolic diseases

Fig 3. Spearman's correlation analysis between DCA, LCA, isoUDCA, isoDCA, 12-epiDCA and 12-oxoDCA in faeces or plasma and clinical parameters.



Correlation analysis of multiple DM-related parameters and DCA levels present. Red indicates a positive correlation, blue indicates a negative correlation. * indicates p-value<0.05, # indicates p-value<0.01.
Left: In the faeces
Right: In the plasma

DISCUSSION

- Low abundant bacterial species *C. scindens* produced large amounts of DCA, which affected insulin tolerance.
- DCA in plasma and faeces correlates with impaired glucose metabolism and worsened lipid profile in individuals with T2DM.

Implications

- The strong correlations between DCA and parameters related to glucose and lipid metabolism suggest that DCA may be a biomarker for inflammation and cardiometabolic diseases.
- Further studies are needed to establish the causality between DCA and metabolic disease - prospective studies may reveal if DCA can be used to identify individuals at risk of developing T2D.

REFERENCES

1. Tan JK, Salim NN, Lim GH, Chia SY, Thumboo J, Bee YM. Trends in diabetes-related complications in Singapore, 2013–2020: A registry-based study. PLOS ONE. 2022 Oct 11;17(10). doi:10.1371/journal.pone.0275920
2. Sadagopan A, Mahmoud A, Begg M, Tarhuni M, Fotso M, Gonzalez NA, et al. Understanding the role of the gut microbiome in diabetes and therapeutics targeting Leaky Gut: A systematic review. Cureus. 2023 Jul 8; doi:10.7759/cureus.41559
3. Crudele L, Gadaleta RM, Cariello M, Moschetta A. Gut microbiota in the pathogenesis and therapeutic approaches of diabetes. eBioMedicine. 2023 Nov;97:104821. doi:10.1016/j.ebiom.2023.104821
4. Wu J, Yang K, Fan H, Wei M, Xiong Q. Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. Frontiers in Endocrinology. 2023 May 9;14. doi:10.3389/fendo.2023.1114424
5. Yehualashet AS, Yikna BB. Microbial ecosystem in diabetes mellitus: Consideration of the gastrointestinal system. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021 Apr 28;Volume 14:1841–54. doi:10.2147/dmso.s304497
6. 2. Razavi S, Amirmozafari N, Zahedi bialvaei A, Navab-Moghadam F, Khamseh ME, Alaei-Shahmiri F, et al. Gut microbiota composition and type 2 diabetes: Are these subjects linked together? Heliyon. 2024 Oct 30;10(20). doi:10.1016/j.heliyon.2024.e39464