



“Digging in the Dirt” faecal microRNAs as dietary biomarkers of host-microbe interactions

Gerard M. Moloney^{1,2^}, John F. Cryan^{1,2^}, Gerard Clarke^{1,3^}

¹Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland; ²APC Microbiome Ireland, University College Cork, Cork, Ireland; ³Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland

Correspondence to: Gerard M. Moloney. Department of Anatomy & Neuroscience, University College Cork, Cork, Ireland. Email: g.moloney@ucc.ie.

Comment on: Tarallo S, Ferrero G, De Filippis F, *et al.* Stool microRNA profiles reflect different dietary and gut microbiome patterns in healthy individuals. *Gut* 2021. [Epub ahead of print]. doi: 10.1136/gutjnl-2021-325168.

Submitted Dec 22, 2021. Accepted for publication Feb 15, 2022.

doi: 10.21037/hbsn-21-551

View this article at: <https://dx.doi.org/10.21037/hbsn-21-551>

The role of diet and nutrition in maintaining a healthy lifestyle has become a central part of chronic disease prevention (1). Chronic conditions such as cancer, Inflammatory bowel disease (IBD) and obesity are more prevalent in people with poor diets (2). Food consumption is controlled by physiological systems such as the gut-microbiome and distinct neuroendocrine pathways that overlap to promote host nutritional gain resulting in people living longer healthier lives (3). A recent analysis of the global burden of disease by the World Health Organization (WHO), noted that factors associated with poor diet, including obesity and malnutrition, critically undermine health and wellbeing. They note that undernutrition, deficiencies in key nutrients and obesity have high social and economic impacts. Cardiovascular disease, cancer, diabetes, and respiratory diseases account for 77% of all diseases and are responsible for 86% of all premature deaths (4). There is an appreciation that diets that reduce or eliminate red meats and animal fats results in the reduction of many of the indicators of poor diet, such as body mass index (BMI) and levels of cholesterol in the blood.

A recent paper published in *Gut* (5), by a multi-disciplinary group led by Dr. Danilo Ercolini and Dr. Alessio Naccarati, analyse faecal samples from a well phenotyped cohort of patients to better understand how different diets affect human health. The composition of the gut microbiota has come under scrutiny as a potential indicator of host health in the general population. Both diversity

and composition are individual- specific and sculpted by habitual dietary habits in both the short and long term (6). Monitoring the composition and function of the contents of stool represents a key targeted strategy in the early diagnosis of disease and general poor health.

Levels of calprotectin and lactoferrin, proteins derived from intestinal neutrophils, are now utilised in the clinic as correlates of disease activity in IBD, prediction of disease flare and response to treatment in both children and adults, with the obvious benefit of avoidance of invasive testing, a particular advantage in the paediatric population (7). Stool represents a harsh environment for molecules due to the high level of bacterial proteases, thus, biomarkers in stool must be durable and robust to survive these conditions. MicroRNAs (miRNAs) represent one such robust molecule. miRNAs are a large family of short non-coding RNAs that are post-transcriptional regulators of gene expression and their detection in peripheral blood offers promise in the areas of cancer and cardiovascular disease detection (8). Using miRNAs as a disease prediction biomarker in faeces is an area that holds much promise (9,10).

Naccarati and colleagues present an exciting paper with a very detailed analysis of the composition of host miRNA signature in circulation and stool, and, importantly, the composition of food-derived miRNAs in stool also. The detailed, careful characterisation of the participants in this study is key to the insights provided. Nutritional intake, along with lifestyle and food frequency will provide valuable

[^] ORCID: Gerard M. Moloney, 0000-0002-3672-1390; John F. Cryan, 0000-0001-5887-2723; Gerard Clarke: 0000-0001-9771-3979.

information to future research in not only this area but other areas, especially when aligned with the sequencing data and food derived miRNA. Impressively, they also utilise an independent cohort of omnivores to repeat this analysis and confirm conclusively their findings in this arm of the study. The authors show that in vegan and vegetarian diets, miR-636 and miR-4739 in the stool, inversely correlate with the length of time each participant had maintained this dietary routine, suggesting that food-derived miRNAs influence the microbiome composition. Further *in-silico* analysis of the target genes of the altered miRNAs suggest that lipid and folate metabolism are at the core of the mechanisms presented.

What is interesting demographically, is that the exercise levels are different between vegetarians and omnivores along with body mass index (BMI), and while the authors do an excellent job of controlling for BMI in the analysis, it points to a few themes not considered by the authors. Firstly, what role does exercise play in the excretion of miRNAs in stool, exercise certainly affects circulating miRNAs (11) and exercise is known to change the composition of the microbiome (12). Furthermore, is the source of the miRNAs in the stool contained within lipids, as their transport is associated with lipids (13) and increased exercise may promote increased shedding of fat in the faeces, future work in this field should explore this possibility. The most exciting work to come in this field will examine the work of Tarallo and colleagues in the context of disease. Could analysing the content of miRNAs in the stool along with the composition of the microbiome be a surrogate marker of nutritional intake in eating disorders, in situations where diet adherence (or non-adherence) is critical to treatment outcome?

An opportunity missed in this analysis is how general mood and anxiety were affected by different dietary regimens (14), and how food-derived miRNAs may be used to edit the microbiome. It is accepted now that the gut microbiome is a viable target for intervention with psychobiotics, prebiotics and probiotics with the aim of improving mental health. It would have been interesting to see if omnivorous, vegetarian, and vegan diets differed in their effects on general mood, anxiety and if length of adherence correlated with mood improvements and possibly peripheral markers of stress, such as cortisol.

Recent advances in omics technology have allowed for an exciting integration of data from multiple disciplines such as transcriptomics, microbiome composition, metabolomics, and non-coding RNAs. The authors have leveraged

numerous datasets and integrated them to produce an impressive picture of how diet can affect multiple pathways within the host. Yet, questions remain. What is the source of microRNAs in the faeces, are they contained within cells, exosomes, attached to lipids, or are they extracellular? If they have come from the colon or ileum, what do they tell us about the environment they have left behind, is it representative or are they “waste”. This field remains in its infancy, but papers like the one discussed here have pushed faecal miRNA to the surface.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-551/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Wang L, Wang H, Wang Z, et al. Interpretation of Healthy Diet Campaign in Healthy China Initiative 2019-2030. *China CDC Weekly* 2021;3:346-49.
2. Schulze MB, Martínez-González MA, Fung TT, et al. Food based dietary patterns and chronic disease

- prevention. *BMJ* 2018;361:k2396.
3. Blanco AM, Calo J, Soengas JL. The gut-brain axis in vertebrates: implications for food intake regulation. *J Exp Biol* 2021;224:jeb231571.
 4. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2019;393:1958–72.
 5. Tarallo S, Ferrero G, De Filippis F, et al. Stool microRNA profiles reflect different dietary and gut microbiome patterns in healthy individuals. *Gut* 2021. [Epub ahead of print]. doi: 10.1136/gutjnl-2021-325168.
 6. Berding K, Vlckova K, Marx W, et al. Diet and the Microbiota-Gut-Brain Axis: Sowing the Seeds of Good Mental Health. *Adv Nutr* 2021;12:1239–85.
 7. Liu F, Lee SA, Riordan SM, et al. Global Studies of Using Fecal Biomarkers in Predicting Relapse in Inflammatory Bowel Disease. *Front Med (Lausanne)* 2020;7:580803.
 8. Raut JR, Schöttker B, Holleczeck B, et al. A microRNA panel compared to environmental and polygenic scores for colorectal cancer risk prediction. *Nat Commun* 2021;12:4811.
 9. Liu S, da Cunha AP, Rezende RM, et al. The Host Shapes the Gut Microbiota via Fecal MicroRNA. *Cell Host Microbe* 2016;19:32–43.
 10. Moloney GM, Viola MF, Hoban AE, et al. Faecal microRNAs: indicators of imbalance at the host-microbe interface? *Benef Microbes* 2018;9:175–83.
 11. Zhou Q, Shi C, Lv Y, et al. Circulating microRNAs in Response to Exercise Training in Healthy Adults. *Front Genet* 2020;11:256.
 12. Mohr AE, Jäger R, Carpenter KC, et al. The athletic gut microbiota. *J Int Soc Sports Nutr* 2020;17:24.
 13. Vickers KC, Palmisano BT, Shoucri BM, et al. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat Cell Biol* 2011;13:423–33.
 14. Berding K, Cryan JF. Microbiota-targeted interventions for mental health. *Curr Opin Psychiatry* 2022;35:3–9.

Cite this article as: Moloney GM, Cryan JF, Clarke G. "Digging in the Dirt" faecal microRNAs as dietary biomarkers of host-microbe interactions. *HepatoBiliary Surg Nutr* 2022;11(2):292–294. doi: 10.21037/hbsn-21-551