Gut Online First, published on February 10, 2018 as 10.1136/gutjnl-2017-315732

Does Akkermansia muciniphila play a role in type 1 diabetes?

Gilles Mithieux[1,2,3]

A field currently attracting increasing interest concerns the possible role that the intestinal microbiota might play in human health and disease. The fact that novel sequencing approaches applied to the microbiota genome are available has definitely favoured the rapid development of this field. The recent re-emergence in this area began with studies on obesity and metabolic diseases. Various associations between microbiota composition and metabolic diseases such as obesity and type 2 diabetes have been reported, in both rodents and humans, emphasising the key role of dietary habits in the composition of the bacterial population.[1–3] However, experiments aimed at changing microbiota composition and transferring/exchanging the intestinal microbiota to alter the metabolism of the host have proved somewhat controversial and failed to unequivocally establish a causal role for the gut microbiota in metabolic diseases.[4] Whatever the case, it is noteworthy that a specific bacterium, *Akkermansia muciniphila*, an abundant constituent of the gut microbiota in healthy humans, has been demonstrated to correct host metabolic disorders when given by gavage as a probiotic in obese insulin-resistant mice.[2] Nowadays, interest in the role of intestinal microbiota in diseases has widened to cover various types of disease like mental disorders,[5] neurodegenerative disorders[6] and immune system disorders,[7] including autoimmune disorders such as type 1 diabetes.[8]

Hänninen *et al* raise the question of the role of the gut microbiota in the pathogenesis of type 1 diabetes in mice.[9] Taking two colonies of non-obese diabetic mice with different diabetes incidence, they report that the colony with high diabetes incidence exhibited reduced bacterial diversity compared with the low incidence colony. In particular, several taxa were absent in the high incidence colony, *A. muciniphila* among them. Interestingly, the abundance of *A. muciniphila* in the gut microbiota had already been reported to negatively correlate with type 1diabetes in mice and humans, suggesting that the bacteria could play a protective role in the development of type 1 diabetes.[10] Restoring bacterial diversity in the high incidence colony by transferring the microbiota from the low incidence colony (by oral transfer or cohousing) failed to delay the occurrence of diabetes. However, *A. muciniphila* was the only bacterial species incapable of establishing in the acceptor after transplantation.[9] Importantly, when this symbiont was orally transferred in mice from the high incidence colony, diabetes occurrence was significantly delayed in the acceptors. This strongly suggests that transferring *A. muciniphila* could protect mice from the development of autoimmune diabetes.

As for the related mechanism, *A. muciniphila* could act locally by reinforcing the gut barrier (compromised in non-obese diabetic mice), possibly by stimulating the production of mucus and thickening the mucus layer. This could prevent its penetration by inflammatory symbionts, hence the reduction of plasma endotoxaemia observed. *A. muciniphila* systemically lowered islet inflammation, promoting Foxp3+ regulatory T cells in islets and interleukin 10 and transforming growth factor-β expression in the pancreatic lymph nodes.[9] This could be a key link in the mechanism by which the transfer elicits regulatory immune signalling to delay diabetes incidence. It is noteworthy that colonisation by *A. muciniphila* induced substantial reshaping in the gut microbiota composition of the acceptor, thereby indicating that other bacterial species could play a role in the benefits resulting from the transfer. Taking this issue still further it would be of great interest to assess whether a protein, previously identified in the membrane of the bacteria and which interferes with innate immune signalling *via* binding to toll-like receptor 2, restores gut permeability and partly reproduces the metabolic benefits conferred by living bacteria in the context of obesity/insulin resistance,[11] could play a role in the protection conferred here.

The account given in *Gut* by Hänninen *et al* is important for several reasons. First, it highlights how fascinating and intriguing microbiota research can be when it goes beyond sequencing the gut microbiome to focus on associations between microbiota composition and health and diseases. Second, it also emphasises how experiments attempting the transfer of the whole microbiota can be misleading as such, whether successful or not, if they are not pursued with well-thought mechanistic questions. Moreover, the limits of statistics in analysing the changes in the gut microbiome in health and diseases have been recently emphasised, due to the interindividual variability and the insufficient sample size of most studies.[12] The possible pitfalls of microbiota transfer in germ-free and/or antibiotic-treated mice, for example, have also been scrutinised.[4 13] Third, an important point addressed in the discussion on the article relates to the thickness and the quality of the mucus layer (see above), which reminds us that the latter segregates the luminal bacteria from the intestinal mucosa, meaning that metabolites and compounds of low molecular weight mostly represent natural communication links between the bacteria and the host, as previously pointed out.[4] A powerful example of this rationale was provided recently *via* the identification of peptides of microbial origin, with anti-inflammatory properties, capable of inhibiting the mucosal nuclear factor-κB pathway.[14] These peptides actually derive from a protein produced by *Faecalibacterium prausnitzii*, a commensal bacterium controlling the pathogenesis of Crohn's disease.[14] Finally, a very interesting hypothesis to be tested is that peptides deriving from the *A. muciniphila* protein exhibiting metabolic benefits in the context of obesity/diabetes[10] could be involved in protection against the pathogenesis of autoimmune diabetes illustrated here. As in numerous diseases, in autoimmune diabetes, the metabolomics of fractions deriving from the gut microbiota could elucidate the various ways in which the bacterial function may interfere with the host's health.

[1]Institut National de la Santé et de la Recherche Médicale, Lyon, Rhône-Alpes, France
[2]Claude Bernard University Lyon 1, Villeurbanne, France
[3]University of Lyon, Lyon, France

Correspondence to Dr Gilles Mithieux, Universite Lyon 1, Faculte de Medecine Lyon-Est, Inserm Laboratory Nutrition, diabetes and the brain, U 1213, Rue Guillaume Paradin, 69372 Lyon, France; gilles.mithieux@inserm.fr

Contributors GM has written the commentary.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Mithieux G. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2017-315732

Received 19 January 2018
Revised 25 January 2018
Accepted 26 January 2018

► http://dx.doi.org/10.1136/gutjnl-2017-314508

Gut 2018;**0**:1–2.
doi:10.1136/gutjnl-2017-315732

REFERENCES

1 Turnbaugh PJ, Bäckhed F, Fulton L, *et al*. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe* 2008;3:213–23.
2 Everard A, Belzer C, Geurts L, *et al*. Cross-talk between akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A* 2013;110:9066–71.
3 David LA, Maurice CF, Carmody RN, *et al*. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014;505:559–63.
4 Mithieux G. Gut microbiota and host metabolism: what relationship? *Neuroendocrinology*. In Press. 2017.
5 Rieder R, Wisniewski PJ, Alderman BL. Campbell SC: microbes and mental health: a review. *Brain Behav Immun*. In Press. 2017.
6 Westfall S, Lomis N, Kahouli I, *et al*. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cell Mol Life Sci*. In Press. 2017;74:3769–87.
7 Levy M, Kolodziejczyk AA, Thaiss CA, *et al*. Dysbiosis and the immune system. *Nat Rev Immunol* 2017;17:219–32.
8 Yurkovetskiy LA, Pickard JM, Chervonsky AV. Microbiota and autoimmunity: exploring new avenues. *Cell Host Microbe* 2015;17:548–52.
9 Hänninen A, Toivonen R, Pöysti S, *et al*. *Akkermansia muciniphila* induces gut microbiota remodelling and controls islet autoimmunity in NOD mice. *Gut* 2017:gutjnl-2017-314508 [Epub ahead of print 21 Dec 2017].
10 Hansen CH, Krych L, Nielsen DS, *et al*. Early life treatment with vancomycin propagates akkermansia muciniphila and reduces diabetes incidence in the NOD mouse. *Diabetologia* 2012;55:2285–94.
11 Plovier H, Everard A, Druart C, *et al*. A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nat Med* 2017;23:107–13.
12 Sze MA, Schloss PD. Looking for a signal in the noise: revisiting obesity and the microbiome. *MBio* 2016;7:e01018–16.
13 Lundberg R, Toft MF, August B, *et al*. Antibiotic-treated versus germ-free rodents for microbiota transplantation studies. *Gut Microbes* 2016;7:68–74.
14 Quévrain E, Maubert MA, Michon C, *et al*. Identification of an anti-inflammatory protein from Faecalibacterium prausnitzii, a commensal bacterium deficient in Crohn's disease. *Gut* 2016;65:415–25.

Does *Akkermansia muciniphila* play a role in type 1 diabetes?

Gilles Mithieux

Gut published online February 10, 2018

Notes