MICROBIOME RESEARCH

Microbial signatures in metabolic tissues: a novel paradigm for obesity and diabetes?

By analysing microbial profiles in three adipose tissue depots and the liver and plasma of morbidly obese individuals, a new study uncovers a unique organ-specific microbial signature, or potential internal 'tissue microbiota', in obese people with diabetes.

Patrice D. Cani and Matthias Van Hul

Visceral fat accumulation is considered one of the most important risk factors for the development of type 2 diabetes. Although the molecular mechanisms linking visceral fat accretion to impaired glucose metabolism are not yet fully elucidated, one commonly accepted trigger is chronic low-grade inflammation in the visceral fat and metabolic organs, such as the liver and muscles, in people with diabetes and obesity[1].

The gut microbiota is a major driver of chronic inflammation, owing to the translocation of different bacterial components, such as lipopolysaccharides, from the gut to the bloodstream; this phenomenon is defined as metabolic endotoxaemia[2]. Although numerous studies have linked the composition and activity of the gut microbiota to metabolic diseases[3], whether the gut microbiota is causally linked to obesity and type 2 diabetes remains a matter of debate. An important limitation in that regard is that most related studies have relied primarily on the analysis of stool microbiota. Few reports have identified potential microbial signatures in the blood or adipose tissue of people with obesity and diabetes[4,5]. However, concerns about potential microbial contamination of samples and false-positive results have shed doubt on the validity of these findings[6].

A new study by Anhê et al., published in this issue of *Nature Metabolism*[7], appears to have successfully overcome this obstacle by carefully controlling for contamination at every step during sampling and analysis, and by providing a comparative and contamination-aware analysis of different microbial profiles. Owing to the large number of controls, the authors succeeded in providing clear and convincing data collection with minimal risk of reporting false-positive results. For example, the 1,000-fold signal difference between tissue samples and negative controls strongly indicates that the data are reliable and reflect the actual microbial load of tissues rather than contamination.

This pioneering work is of utmost interest to the scientific community. Indeed, this study is the first investigating microbial signatures by using 16S ribosomal RNA (rRNA) gene-based bacterial quantification in plasma and at different body sites, particularly key metabolic organs that are notoriously difficult to access, including the liver and the visceral and omental fat depots (Fig. 1). Another original aspect of this work is that the authors focused their analysis on a potential specific inter-organ microbial signature that is independent of the body mass index, as well as its links to glycaemia and diabetes.

Interestingly, the researchers found higher copy numbers of the 16S rRNA gene in the omental adipose tissue and liver than in the mesenteric, subcutaneous and plasma compartments (Fig. 1). Proteobacteria was the dominant phylum in all five tissues studied, although the data also provide evidence of tissue-specific bacterial compartmentalization. Among the bacterial signatures, *Pseudomonas* was the predominant genus across all tissues, although a higher number of 16S rRNA gene copies was observed in organs than in plasma. *Arthrobacter* and *Ruminoccocus*, in contrast, were preferentially found in the liver. Eight other genera were more prevalent in the three adipose tissues. Whereas *Bacteroides*, *Faecalibacterium* and *Enterobacter* were present in adipose tissues and are classically representative of the gut microbiota, the other detected genera are primarily considered environmental bacteria, which are commonly found in soil or water (Fig. 1). In addition, the finding that many of the bacteria appear to come from not only the gastrointestinal tract but also other sources—such as food, water or soil—strongly suggests that our internal organs are constantly exposed to potential foreign genetic signatures.

A compromised gut barrier function has been linked to obesity and diabetes[8,9]. However, in the current study, it remains unclear whether these 16S rRNA gene signatures reflect real bacterial translocation to the various internal tissues or whether the deposition of genetic material is a result of active sampling of intestinal or luminal content by cells of the immune system, including dendritic cells or M cells (Fig. 1). Evaluation of the gut microbiota composition of the individuals involved in this study could have shed light on this matter. However, although the lack of information about the gut microbiome might be considered a missed opportunity, it does not diminish the relevance of the overall findings, and the study should be regarded for what it is: pioneering work that paves the way for future studies attempting to link microbial signatures of different organs to the gut and mucosal microbiota. Furthermore, given the presence of environmental microbial signatures in internal tissues, investigating the potential origin and source of these signals would be of interest.

Another intriguing finding is that, despite having the same body mass index and the same number of 16S rRNA gene copies within each tissue, the participants with type 2 diabetes, compared with participants in the obese non-diabetic group, displayed different microbial signatures with higher Enterobacteriaceae (that is, *Escherichia* and *Shigella*) in the plasma and mesenteric adipose tissue. This observation not only supports previous findings suggesting a potential role of metabolic endotoxaemia at the onset of diabetes but also corroborates data showing higher abundance of *Escherichia* and *Shigella* in the faeces of dysglycaemic individuals compared with normoglycaemic individuals. The authors also observed lower microbial diversity in the mesenteric adipose tissue as well as lower abundance of various bacteria

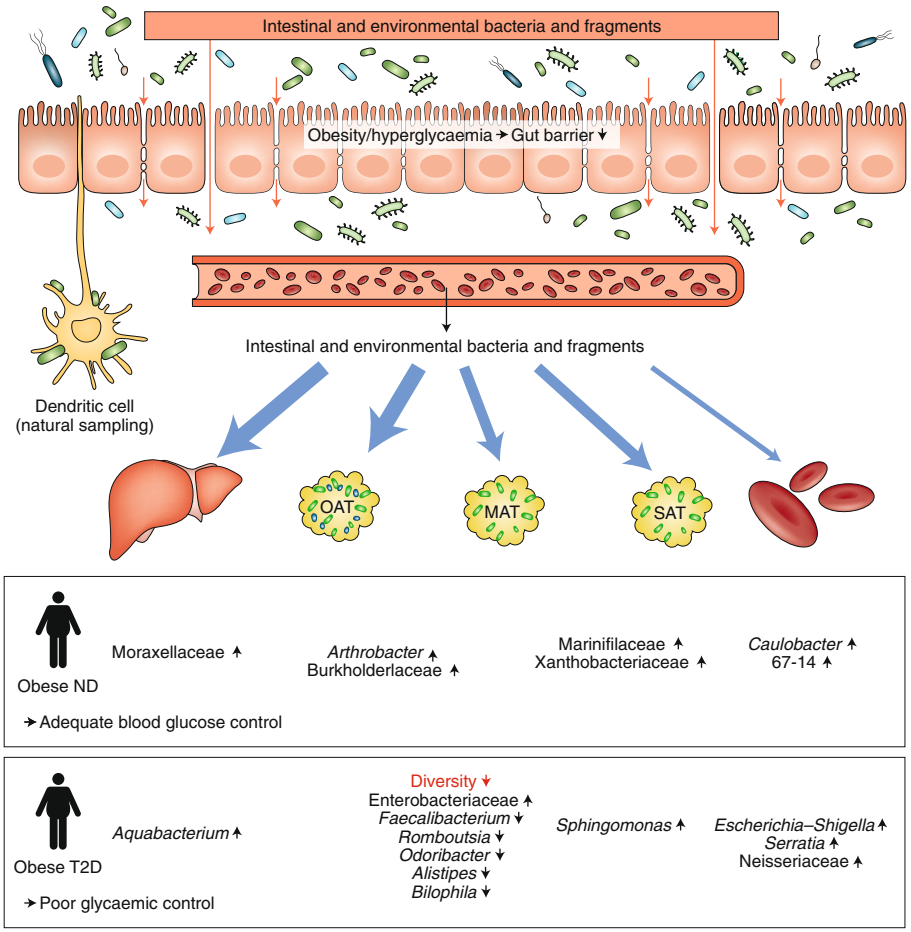

Fig. 1 | Bacterial compartmentalization in obese and diabetic individuals. Intestinal and environmental bacteria and fragments are physiologically sampled from the intestinal lumen by immune cells, such as M cells or dendritic cells, or they can translocate into the blood and subsequently reach different tissues. Bacterial signatures are found in the liver, omental adipose tissue (OAT), mesenterial adipose tissue (MAT), subcutaneous adipose tissue (SAT) and blood. The different taxa and their abundance (that is, higher or lower levels in obese non-diabetic (ND) versus obese type 2 diabetic (T2D) individuals) in tissues are indicated. The relative abundance of bacterial deposits is relatively higher in tissues along the anatomical route from the gut to the liver, and relatively lower in subctutaneous adipose tissue and peripheral blood (represented by the thickness of the blue arrows).

from the phyla Firmicutes, Bacteroidetes and Deltaproteobacteria in participants with type 2 diabetes than in non-diabetic participants. This finding also suggests that the extra-intestinal microbial signature may dictate the type 2 diabetes status through a mechanism that appears to be independent of obesity. The extent to which this microbial signature is linked to the metabolic state or potential antidiabetic drug treatments warrants further investigation.

In conclusion, Anhê et al. have elegantly provided intriguing evidence of bacterial genetic signatures in five extra-intestinal biological compartments. This pioneering and laudable achievement is a true game changer for the field of microbiome research and represents exactly the type of paradigm shift that the field needs. As such, this study could be the first in a new line of research that will progressively increase knowledge and help to decipher the role of the 'tissue microbiota', its interactions with the host, and its relevance to metabolic and potentially other diseases. ❐

Patrice D. Cani and Matthias Van Hul
UCLouvain, Université catholique de Louvain, Walloon Excellence in Life Sciences and Biotechnology (WELBIO), Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Brussels, Belgium.
✉*e-mail: patrice.cani@uclouvain.be*

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Competing interests

P.D.C. is an inventor in patent applications related to the use of *Akkermansia muciniphila* and its components in the context of obesity and related disorders. P.D.C. is also a co-founder of A-Mansia Biotech SA. M.V.H. declares no conflicts of interest.