When specific gut microbes reveal a possible link between hepatic steatosis and adipose tissue

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The gut microbiota is considered as a factor involved in the regulation of numerous metabolic pathways by impacting different functions of the host. Among these regulations, the influence of gut microbes on energy homeostasis is of particular interest because it has been suggested to be a driving force in the pathogenesis of metabolic diseases associated with obesity (such as insulin resistance, diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD)) [1,2]. Intestinal microbes have developed a mutualistic relationship with their host and can influence physiological systems by modulating gut motility, intestinal barrier homeostasis, nutrient absorption, fat distribution, and liver fat accumulation [3,4].

The relationship between changes in gut microbiota and the development and progression of liver disease has been known for over fifty years. Endotoxemia and gut-derived toxins are suggested to have causative roles in the onset and progression of liver inflammation and damage in chronic liver diseases [5]. Similar to the mechanisms underlying metabolic endotoxemia (i.e., increased blood lipopolysaccharides (LPS) levels) and inflammation described in our previous work [6], intestinal bacterial overgrowth, gut leakiness and increased endotoxin absorption have all been associated with hepatic fat accumulation and inflammation (NAFLD and non-alcoholic steatohepatitis (NASH)) in both rodents and human patients [7–9]. However, the role of specific bacteria, metabolites coming from the gut microbiota or both remained to be demonstrated.

In NAFLD patients changes in tight junction protein expression and distribution are suggested as critical factors in the impairment of gut barrier function and subsequent alterations in gut permeability [10]. As a consequence, metabolic endotoxemia exposes the liver to gut-derived toxins resulting in the release of numerous pro-inflammatory cytokines that ultimately lead to hepatic injury and fibrosis [11]. However, although previous studies have shown that the treatment with antibiotics or loss of endotoxins receptors (Toll-like receptor-(TLR) 4) significantly attenuates the development of hepatic steatosis in mice [12,13], it has also been suggested that other TLRs than TLR4 contributed to the onset of NAFLD [14]. In light of these recent findings, understanding the role of specific microbes or microbial communities as well as identifying the cross-talks existing between organs and the gut microbiota related to metabolism regulation is of the utmost importance.

The present study by Munukka et al. in this issue of the Journal of Hepatology provides a putative link between the abundance of one specific bug, namely Faecalibacterium prausnitzii, hepatic fat accumulation and adipose tissue inflammation. By using proton magnetic resonance spectroscopy (1H MRS) they classified their population comprising of 31 subjects into two distinct groups, that is high hepatic fat content (>5%, n = 10) and low hepatic fat content (<5%, n = 21). Munukka et al. also investigated whether hepatic fat content was associated with body composition, adipose tissue inflammation (by microarray) and specific gut microbes (by 16S rRNA hybridization and flow cytometry). The major limitations of this study rely on the fact that the number of patients was relatively small and more importantly because of the use of a targeted approach to investigate the gut microbiota. But, besides these points, the authors found that a lower abundance of F. prausnitzii is associated with hepatic fat accumulation. Moreover, this remained significant after adjustment for gender, age and weight, which reinforce a putative link between this bacterium and host metabolism.

Conversely with previous reports [15], they found that the abundance of the Bacteroides group was positively correlated with insulin resistance index (HOMA-IR). When they combined the data obtained for F. prausnitzii and Bacteroides as a ratio (F. prausnitzii/Bacteroides), the authors found that the level of several genes expressed in the subcutaneous adipose depots and related with inflammation were negatively associated with this ratio. Interestingly, no significant differences were found at the level of several genes involved in lipid metabolism. It is worth noting that in the present study the authors had access to subcutaneous adipose tissues which is likely less prone to directly induce an overflow of the liver with fatty acids, and this in comparison with the visceral adipose-derived fatty acids. Thus, given that in this study the patients with a higher liver fat accumulation exhibited more visceral fat accumulation (2-fold more) it is likely that both type of fat depots contribute to the development of hepatic fat accumulation via complementary mechanisms, that are directly or indirectly associated with the gut microbiota. Nevertheless, in this study Munukka et al. unequivocally found that the
increased inflammatory tone observed in the subcutaneous adipose tissue was correlated with the presence of *F. prausnitzii* and *Bacteroides* and eventually suggest a link between the gut, subcutaneous adipose tissue, and liver fat accumulation.

Although this direct link was not shown in the present study, it has been previously demonstrated that higher abundance of *F. prausnitzii* was associated with an improved inflammatory status in obese patients [16]. Moreover, a reduction in a cluster of genes belonging to *F. prausnitzii* was identified as a discriminant marker for the prediction of diabetic status in European women [17], which may support the link with *F. prausnitzii* observed in the present study and HOMA-IR. Moreover, rodent studies have clearly associated the role of *F. prausnitzii* with intestinal barrier function [18].

Strikingly, the decreased abundance of several genera including *Bacteroides* (which was decreased in the present study) and *F. prausnitzii* has also been found in type 2 diabetic Chinese subjects [19]. Moreover, Balamurugan et al. found that *F. prausnitzii* was increased in obese Indian children compared to the lean controls [20]. Thus these discrepancies strongly highlight once again that the specificity of the population, age, and diets in phenotype and taxonomy associations have to be taken into account before drawing any clear conclusions on the role of one specific bacterium on the onset or the protection against metabolic disorders associated with fat accumulation.

Growing evidence suggests that cross-talks between gut microbes and the host are achieved through specific metabolites such as for example short chain fatty acids or specific molecular patterns of microbial membranes (e.g., LPS) that may contribute to the activation of TLR’s.

In this study, Munukka et al. found a positive association between Enterobacteriaceae family (i.e., Gram negative bacteria) and triglycerides, but they did not find any differences in metabolic endotoxemia measured in the peripheral blood of both groups. Besides the fact that measuring blood LPS is highly tricky, and may be an important confounding factor here, previous studies have clearly associated plasma LPS levels with triglycerides [21].

Thus, in this study, we may not exclude that numerous parameters may have contributed to the regulation of hepatic fat accumulation. Is the phenotype starting from the gut barrier dysfunction and eventually linked with the presence of LPS or any other molecular patterns of microbial membranes? Is the higher inflammatory tone observed in the adipose tissue directly or indirectly associated with any modification of the gut barrier function, or changes in the gut microbiome or both? What is the abundance of other gut bacteria measured by using high-throughput methods (e.g., sequencing)? All these questions remain still unanswered, and merit further investigations.

**Conflict of interest**

The author declare that he not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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**References**


