Approximately 25% of the adult population in Western countries has fatty liver disease, in the absence of excessive alcohol consumption, a condition known as nonalcoholic fatty liver disease (NAFLD). NAFLD is the result of triglyceride accumulation in the hepatocyte and is considered to be the hepatic component of the metabolic syndrome [1]. It is closely related to obesity, insulin resistance and type 2 diabetes mellitus, representing one of the leading causes of chronic liver disease worldwide and the third leading cause of hepatocellular carcinoma. The term NAFLD encompasses different states of disease activity, ranging from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma [1].

The human microbiome consists of the genetic context of bacteria, archaea, viruses and eukaryotic microbes that reside throughout the human body. However, practically the gut microbiome refers to the > 10^{14} bacteria inhabiting the human intestine. Healthy adults harbor more than 1000 species of bacteria, among which Bacteroidetes and Firmicutes are the most prevalent [2]. These microorganisms, which are implicated in various metabolic activities, protect against pathogens and educate the innate system, thus contributing to health or disease, as characterized by homeostasis or dysbiosis, respectively [3].

The liver and the gut are metabolically interconnected. Therefore, any dysfunction in the gut-liver axis, such as increased intestinal permeability and inflammation are associated with NAFLD. NAFLD has been documented to be transmissible after fecal transplantation of the gut microbiome into recipient mice. Also, many animal and human studies have demonstrated the presence of gut dysbiosis in NAFLD. However, findings are conflicting regarding the observed differences in bacterial taxonomic composition amongst various studies. These discrepancies may be due to differences in the: 1) design of the study; 2) studied ethnic groups; 3) studied geographical areas (Asia, Europe, North America); 4) age of patients, i.e. adults versus children; 5) sample size; 6) laboratory methodologies analyzing gut microbiome as well as 7) the insufficient documentation of liver disease due to the fact that liver biopsy, an invasive diagnostic tool, had been performed only in a few patients [4].

In some studies, NAFLD patients, in particular those with steatohepatitis, exhibit enhancement in Bacteroidetes, decreases in Firmicutes and higher proportions of the Escherichia and Prevotella genera in their gut microbiota (Fig. 1) [4]. Other studies have shown a decrease in butyrate-producing Ruminococcaceae in patients with NAFLD. Notably, the number of Bacteroidetes has been related to lower levels of short chain fatty acids (SCFAs) in mice. SCFAs, which are important microbial metabolites, may exert a beneficial role in hepatic metabolism through: 1) the amelioration of the gut barrier function; 2) the inhibition of the entry of toxic substances such as pro-inflammatory molecules and ethanol to the liver; 3) the suppression of inflammation based on the enhanced differentiation of anti-inflammatory T regulatory cells in the intestine [4]. Nevertheless, data linking gut microbial metabolites to NAFLD are limited in humans, mainly due to the fact that only a minority of patients who underwent liver biopsy are included in clinical trials.

Potential mechanisms by which the gut microbiome could participate in NAFLD pathogenesis include: 1) increased intestinal permeability and inflammation; 2) bile acid metabolism dysfunction; 3) anaerobic fermentation; and 4) insulin resistance through activation of Toll-like receptor-4 (TLR4) by bacterial lipopolysaccharide (LPS). It is noteworthy that patients with NAFLD exhibit increased plasma LPS levels than controls, while patients with NASH present even higher levels being associated with Tumor Necrosis Factor-α (TNF-α) mRNA expression in hepatic tissue, underscoring the role of endotoxemia in NAFLD [4].

Moreover, studies involving the administration of prebiotics or probiotics or symbiotics provide evidence for the implication of gut microbiota in the pathogenesis of NAFLD. Specifically, diet supplementation with the prebiotics fructooligosaccharides in patients with NASH and oral intake of the symbiotics Bifidobacterium longum and fructooligosaccharide in patients with NAFLD were associated with lower levels of serum insulin, liver enzymes, TNF-α, LPS and decreases in steatosis and NASH activity index [5].

In summary, there is no definitive evidence whether gut microbiome and its microbial metabolites are causally associated with NAFLD in humans. Whether gut dysbiosis provokes NAFLD or whether NAFLD causes dysbiosis remains unclear. Further randomized controlled trial and large prospective studies, including well-defined cohorts using more sophisticated, noninvasive diagnostic techniques and a multi-omics approach would better clarify the associations between the gut microbiome and the various liver phenotypes seen in NAFLD.
Fig. 1. The changes in the gut microbiota composition in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) according to most studies.

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