



Mini Review

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Insights in Gut Microbiota and Non-Alcoholic Fatty Liver Disease



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Abstract

Gut microbiota play a critical role in the development of metabolic diseases such as non-alcoholic fatty liver disease (NAFLD), which is a critical public health issue worldwide. This mini review provides new insights in the association between gut microbiota and liver disease, in order to gain better grasp of microbiota-related metabolic pathways and try to establish the key microbes that are implicated in NAFLD progression. It gives better knowledge to understand a possible cause of this disease and to be closer on the development of new diagnosis and therapies.

Keywords: Non-alcoholic fatty disease; Obesity; Gut microbiota; Steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) is a growing public health issue and the most common liver disorder in Western countries [1] and some Asian countries [2]. The global prevalence of NAFLD has been estimated to be 25% [3] and it is closely associated with metabolic syndrome comorbidities [2,4], such as type 2 diabetes, hyperlipidemia, hypertension and also obesity [1,3]. It has been described the prevalence of NAFLD in obese adults to be 67.5% and in diabetic adults, 74% [5]. NAFLD is a pathology with a broad spectrum of liver severity, ranging from simple steatosis (SS) to non-alcoholic steatohepatitis (NASH). SS is characterized by the accumulation of lipid droplets that exceed 5% of the total liver weight. Whilst, NASH is defined as the beginning stages of inflammation and lobular ballooning that cause chronic hepatic injury [6]. The prevalence of NASH in total NAFLD patients is 30%, which can progress to fibrosis and also cirrhosis [7,8]

The manifestation and progression of NAFLD was elucidated by the “double-hit” hypothesis. The “first hit” was attributed to the accumulation of lipids in the hepatocytes; diagnosed as SS. This was followed by the “second hit” which was described as the onset of the inflammation process and hepatocellular injury; diagnosed as NASH [8,9]. However, “multiple hit” hypothesis is currently accepted, because of its better understanding of molecular pathways [10]. This hypothesis considers several

simultaneous factors, such as altered gut microbiota, that are crucial for the development of metabolic diseases and also NAFLD. While intestinal microbiota had been widely accepted to play an important role in human health and disease, especially in the pathophysiology of obesity, it is not clearly understood the impact of gut microbiota to the progression of NAFLD. However, previous studies had established small intestinal bacterial overgrowth and gut microbiota dysregulation to be the main factors involved in NAFLD development.

The accumulation of fat in the liver is probably caused by the dysregulation of energy homeostasis, and bile acid and choline metabolism due to gut microbiota changes [11]. Energy homeostasis is highly controlled by gut microbiota, which can stimulates lipogenesis, and causes the accumulation of triglycerides in adipose tissue resulting in obesity and NAFLD development. Additionally, bile acids are molecules which regulate the homeostasis of triglycerides, cholesterol and glucose in the liver, and choline plays an important role in lipid metabolism and enterohepatic circulation of bile acid and cholesterol metabolism. Therefore, the dysregulation of bile acid and choline metabolism can contribute to the accumulation of fat in the liver.

Regarding to liver inflammation process in NAFLD, the main molecules implicated on that are pro-inflammatory cytokines

from adipose tissue and gut-derived endotoxins [12] which cause the dysregulation of the innate immunity system [9]. Therefore, the composition and microbiome abundance are critical factors in NAFLD progression.

A huge biodiversity of bacteria is present in human intestine, however only four phylums dominate it; *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* [13]. A prospective cross sectional study had shown lower *Bacteroidetes* levels in NASH obese patients compared with SS and controls with lower body mass index (BMI) [14]. Studies of obese subjects could be a big confounder in the association of gut microbiota and NAFLD, since it has been demonstrated BMI to be a major cause of intestinal dysbiosis. Therefore, Wang et al. [2] had performed a prospective cross-sectional study which compared the fecal microbiota of nonobese adult patients with and without NAFLD, (n=43, n=83, respectively). It was found lower diversity and phylum-level change; 20% more phylum and 24% less *Firmicutes*, in nonobese NAFLD compared with lean healthy controls. Both studies have found a link between gut microbiota and the presence of NAFLD, however they did not find similar differences in gut microbiota strains.

Nowadays, the therapy of NAFLD is considered to be lifestyle changing and diet intervention [15], including prebiotic and probiotic supplementation, due to their capability to modulate gut microbiota. An experimental study realized with Zucker obese rats showed a protective effect against hepatic steatosis of *Lactobacillus paracasei*, *Bifidobacterium breve*, *Lactobacillus rhamnosus* and a mixture of *L. paracasei* and *B. breve* supplementation. Triacylglycerol liver content, tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and lipopolysaccharide (LPS) plasma levels decreased in the Zucker obese rats [16]. These data suggest that NAFLD amelioration by probiotic strains could be due to their anti-inflammatory effects.

In conclusion, gut microbiota play a critical role in the pathogenesis of NAFLD, nevertheless more experimental evidence is required to establish a stronger association between specific intestine bacterial strains and the progression of NAFLD. If the key microbes and their metabolic pathways can be established, dietary intervention and other therapies could change gut microbial composition and, therefore, ameliorate NAFLD.

Conflict of interest

The authors declare no conflict of interest.

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