Review article:

NONALCOHOLIC FATTY LIVER DISEASE, DIET AND GUT MICROBIOTA

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a severe liver disease that is increasing in prevalence with the worldwide epidemic of obesity and its related insulin-resistance state. Evidence for the role of the gut microbiota in energy storage and the subsequent development of obesity and some of its related diseases is now well established. More recently, a new role of gut microbiota has emerged in NAFLD. The gut microbiota is involved in gut permeability, low-grade inflammation and immune balance, it modulates dietary choline metabolism, regulates bile acid metabolism and produces endogenous ethanol. All of these factors are molecular mechanisms by which the microbiota can induce NAFLD or its progression toward overt non-alcoholic steatohepatitis. Modification of the gut microbiota composition and/or its biochemical capacity by specific dietary or pharmacological interventions may advantageously affect host metabolism. Large-scale intervention trials, investigating the potential benefit of prebiotics and probiotics in improving cardiometabolic health in high-risk populations, are fervently awaited.

Keywords: Gut microbiome, NAFLD, interventions

INTRODUCTION

The rising incidence of obesity in today's environment is associated with many obesity-related health complications, including cardiovascular disease, type 2 diabetes (T2D), hyperlipidemia, hypertension, and nonalcoholic fatty liver disease (NAFLD) (Tarantino et al., 2007; 2012; 2013; Finelli and Tarantino, 2013a). This constellation is also recognized as the metabolic syndrome and is characterized by underlying insulin resistance (IR). NAFLD or generally speaking hepatic steatosis (HS) is defined as the accumulation of lipid, primarily in the form of triacylglycerols in in-

dividuals who do not consume significant amounts of alcohol (< 20 g ethanol/d) and in whom other known causes of steatosis, such as certain drugs and toxins, have been excluded (Vuppalanchi and Chalasani, 2009). The spectrum of NAFLD includes simple fatty liver, non alcoholic steatohepatitis (NASH) - characterized by inflammation, apoptosis, ballooning degeneration, Mallory hyaline, fibrosis-, cirrhosis post NASH, hepatocellular carcinoma and advanced liver disease, which leads to liver-related death (Vuppalanchi and Chalasani, 2009; Sorrentino et al., 2004; Tarantino and Finelli, 2013; Tarantino, 2007; Tarantino et al., 2011a; Finelli and Tarantino, 2013c).

Given the close relations between obesity, the metabolic syndrome, and the development of NAFLD, it is not surprising that many NAFLD patients have multiple components of the metabolic syndrome, whether or not they are overweight or obese. IR is present in and is a significant predictor of NAFLD and NASH in most patients (Clark, 2006), even the ~ 10–15 % of patients who are not overweight (Chiang et al., 2011; Hamaguchi et al., 2012). NAFLD is a multifactorial disease that involves a complex interaction of genetics, diet, and lifestyle, all of which combine to form the NAFLD phenotype. A cornerstone of the management strategy in such patients with fatty liver is the use of diet to decrease body weight, and improve glycemic control, dyslipidemia and cardiovascular risks as well (Finelli and Tarantino, 2012b).

Gut microbiota are thought to play a role in the pathogenesis of NASH for several reasons. First, gut microbiota are known to have a large effect on the digestion and absorption of nutrients (van der Hoeven-Hangoor et al., 2013). Microbiota transplantation experiments in mice suggested that certain microbiota is capable of inducing obesity independent of other environmental factors (Kallus and Brandt, 2012). Second, gut microbiota participate in the development and homeostasis of the overall immunity of the host (Gigante et al., 2011). Therefore, certain microbiota may influence the development of liver inflammation. The links between gut microbiota and the host immune system include TLRs and short-chain fatty acids (Vinolo et al., 2011). In fact, the innate immune system might influence the metabolic syndrome and obesity, as mice deficient in Toll-like receptor 5 develop hyperphagia, become obese and insulin resistant (Tilg, 2010). Third, gut microbiota may influence the production of gut hormones, such as glucagon-like peptide 1, and, subsequently, have an effect on the overall metabolism of the host (Flint, 2011).

The liver appears as the first point of contact for (and produces the initial immunological response to) bacteria and microbial components, as well as other endogenous and exogenous toxins present in the portal blood. Given the capacity of the liver to regulate metabolism in a form that can affect the entire organism, to distribute numerous substances to the gut through bile and the entero hepatic circulation, and to regulate numerous hormonal and immunological responses, the potential for the liver to influence gut function can be quickly appreciated. Interactions between the gut, the diet and the liver are, naturally, bidirectional; hormones, inflammatory mediators and the products of digestion and absorption all unequivocally influence liver function. The focus of this review is on gut–liver-diet interactions that contribute to the pathogenesis of a common liver disorder, NAFLD.

Interactions between the intestinal microbiota and liver

The interactions of the gut microbiota and the liver have only recently been investigated in detail. Receiving approximately 70 % of its blood supply from the intestinal venous outflow, the liver represents the first line of defense against gut-derived antigens, food antigens, toxins, microbial-derived products, and microorganisms (Henao-Mejia et al., 2013). The liver, therefore, is equipped with a broad array of immune cells (i.e., macrophages, lymphocytes, natural killer cells, and dendritic cells) to accomplish this function (Henao-Mejia et al., 2013). Small intestinal bacterial overgrowth (SIBO) is common in patients with cirrhosis (Wiest et al., 2014; Savarino et al., 2011; Bellot et al., 2013; Gupta et al., 2010) and its prevalence correlates directly with the severity of liver disease (Pande et al., 2009). A physiological basis for SIBO in liver disease was added by reports of impaired small bowel motility and prolonged orocecal transit time in patients with cirrhosis (Seo and Shah, 2012; Gunnarsdottir et al., 2003). Some studies reinforced the con-

cept that disturbed motility predisposes to SIBO, and suggested a link between alterations in intestinal motility and the development of both hepatic encephalopathy and spontaneous bacterial peritonitis (Romeiro et al., 2013; Ancel et al., 2006; Bouin et al., 2004; Garcovich et al., 2012). Bacterial translocation (passage of viable bacteria resident in the gastrointestinal tract to generally sterile tissues) in the context of SIBO is facilitated by augmented intestinal permeability, another feature of liver cirrhosis (Hada et al., 2010; Cariello et al., 2010). Indeed, increased intestinal permeability is associated with an increased risk of spontaneous bacterial peritonitis (Benjamin et al., 2013; Assimakopoulos et al., 2012).

Having identified bacterial products as hepatotoxins (Lamontagne et al., 2013; Kisch et al., 2006) and having figured out that multiple metabolic activities of the gut microbiota could affect the liver function, the potential for the gut microbiota to induce or maintain various liver diseases, mainly at the light of its immunological interactions with the host has been clearly reckoned.

Nafld, intestinal microbiota and metabolic changes

NAFLD is a multifactorial disease. Numerous genetic, metabolic, inflammatory and environmental factors are consideration to contribute to its pathogenesis (Figure 1). In the middle of the environmental factors, diet is the most important, though its role may be more complex than one of simply inducing fat accumulation in the liver, and may involve interactions with the microbiota. indeed, the microbiota may contribute to NAFLD in a number of ways, some of which are quite unexpected.

Obesity

Obesity, especially visceral obesity, is a major risk factor for NAFLD in humans (Finelli and Tarantino, 2012a). The gut microbiota is partly responsible for body fat

deposition in mice (Flint, 2011). Usually colonized animals have a higher body fat content than do germfree animals; the inoculation of germfree mice with micro biota obtained from usually colonized adult animals resulted in a 57 % increase in total body fat (Wolf, 2006). Organisms in the Bacteroidetes and Firmicutes phyla collectively represent about 90 % of the microbiota composition in mice, as they do in humans (Murphy, 2010). However, their relative contributions vary considerably according to body composition. In a murine model, it was shown that the relative abundance of these two phyla differs among lean and obese mice; the obese mouse had a higher proportion of Firmicutes to Bacteroidetes (50 % greater) than the lean mouse (Kallus and Brandt, 2012). The same results were appreciated in obese humans compared to lean subjects, as reported by Kallus and Brandt (2012). The postulated explanation for this finding is that Firmicutes produce more complete metabolism of a given energy source than do Bacteroidetes, thus promoting more efficient absorption of calories and subsequent weight gain (Kallus and Brandt, 2012). These findings indicate a possible role for components of the microbiota in determining the efficiency of calorie extraction from the diet and, thereby, influencing body weight (Blaut and Klaus, 2012). It showed that the significant increase in mannitol excretion rate, in patients undergoing Roux-en-Y Gastric Bypass (RYGB), from the first postoperative month to the sixth postoperative month most likely reflects the occurrence of intestinal adaptation (mucosal hyperplasia), which would tend to minimize the malabsorption of macronutrients (Savassi-Rocha et al., 2014). A subgroup of patients who undergo RYGB exhibit pronounced increase in their intestinal permeability (assessed by the lactulose/mannitol ratio and the lactulose excretion rate) at the sixth postoperative month (Savassi-Rocha et al., 2014). Obese humans harbour considerably
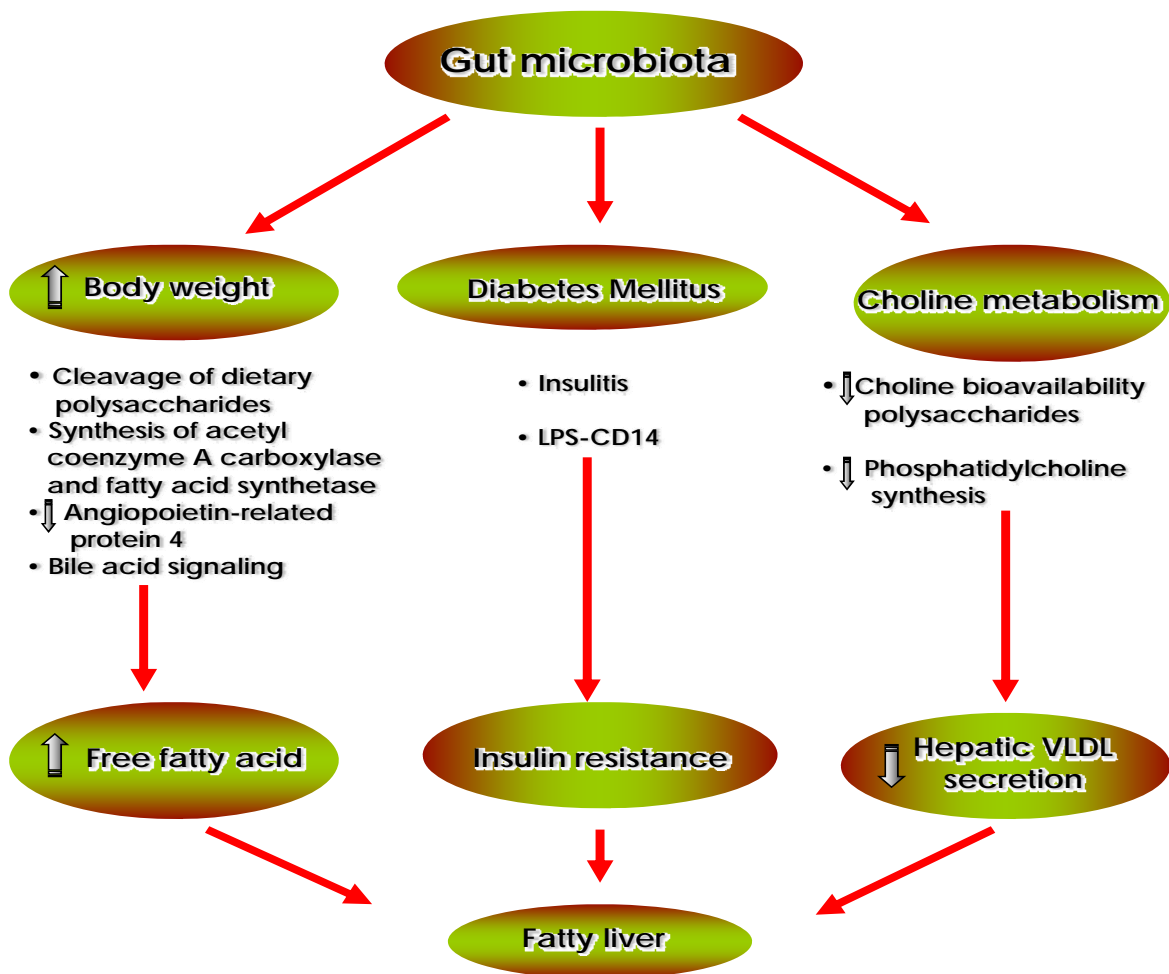
Figure 1: Effects of the gut microbita on pathogenesis of NAFLD
(Abbreviations: LPS – lipopolysaccharide; VLDL – very-low-density lipoprotein)

fewer Bacteroidetes and more Firmicutes than lean controls (Krznarić et al., 2012). Changes in the gut microbiota have also been documented among obese individuals after gastric bypass surgery (Osto et al., 2013). Osto et al. (2013) showed that RYGB surgery might differently modify the gut microbiota composition in the three distinct anatomical sections of the small intestine compared to sham surgery. RYGB induced changes in the microbiota of the alimentary limb and the common channel resembling those seen after prebiotic treatment or weight loss by dieting, as reported by Osto et al. (2013). These changes may be associated with altered production of intestinal hormones known to control energy balance (Osto et al., 2013). Postsurgical modulation of gut microbiota may significantly contribute to the beneficial metabolic effects of RYGB surgery (Osto et al., 2013), not excluding those on NAFLD.

Santacruz et al. (2009) indicated that calorie restriction and physical activity have an impact on gut microbiota composition related to body weight loss, which also seem to be influenced by the individual's microbiota. Limited evidence suggests a role for increased microbial extraction of calories among obese humans. DiBaise et al. (2008), in their review, suggests that the gut microbiota affects nutrient acquisition and energy regulation and its composition has also been shown to differ in lean vs obese animals and humans. Some evidence suggests that the metabolic activities of the gut microbiota facilitate the extraction of calories from ingested dietary substances

and help to store these calories in host adipose tissue for later use (DiBaise et al., 2008). Furthermore, the gut bacterial flora of obese mice and humans include fewer Bacteroidetes and correspondingly more Firmicutes than that of their lean counterparts, suggesting that differences in caloric extraction of ingested food substances may be due to the composition of the gut microbiota (DiBaise et al., 2008). Bacterial lipopolysaccharide derived from the intestinal microbiota may act as a triggering factor linking inflammation to high-fat diet-induced metabolic syndrome (DiBaise et al., 2008). DiBaise et al. (2008) concluded that existing evidence warrants further investigation of the microbial ecology of the human gut and points to modification of the gut microbiota as one means to treat people who are over-weight or obese.

Several studies reveal how the microbiota might influence body weight and composition. Gut microbiota could precisely affect the proportion of calories obtained from the intestinal contents (caloric salvage). For example, *Bacteroides thetaiotamicron* is able to break most glycosidic linkages of numerous constituents of our diet. This Gram-negative anaerobic bacterium can degrade indigestible poly saccharides from plant, representing a quota part of calorie needs, nearly 10–15 % (Zocco et al., 2007). Furthermore, microbes are predominantly found in surface-attached and spatially structured polymicrobial communities (Estrela and Brown, 2013). Within these communities, microbial cells excrete a wide range of metabolites, setting the stage for interspecific metabolic interactions (Estrela and Brown, 2013). The links, however, between metabolic and ecological interactions (functional relationships), and species spatial organization (structural relationships) are still poorly understood, as reported by Estrela et al. (2013). It showed that strong metabolic interdependence drives the emergence of mutualism, robust interspecific mixing, and increased community productivity. These emergent community properties are driven by demographic feedbacks, such that aid from neighboring cells directly enhances focal cell growth, which in turn feeds back to neighbour fecundity. In contrast, weak metabolic interdependence drives conflict (exploitation or competition), and in turn greater interspecific segregation. Together, these results support the idea that species structural and functional relationships represent the net balance of metabolic interdependencies (Estrela and Brown, 2013).

The caloric restore is furnished by the presence of genes encoding enzymes that split vegetable and dietary polysaccharides in the microbiota of obese mouse. Administration of a conventional microbiota to germ free mice induced a rapid increase in body fat associated with increased hepatic triglyceride production related to increased activity of two crucial enzymes involved in de novo fatty acid synthesis—acetyl coenzyme a carboxylase and fatty acid synthetase (Wolf, 2006). The microbiota inhibits angiopoietin related protein 4, which suppresses lipoprotein lipase, a key regulator of fatty acid release from triglyceride rich chylomicrons. Inhibition of angiopoietin related protein 4 causes hyper-expression of lipoprotein lipase, giving place to an augmented uptake of fatty acids and storage of triglycerides in adipocytes (Wolf, 2006; Fleissner et al., 2010) and liver (Fleissner et al., 2010).

Gut microbes have a pivotal role in the intra luminal metabolism of bile acids (Ruiz et al., 2013). Given that bile acids are fundamental for the absorption and emulsification of dietary fats and lipid soluble vitamins in the small intestine, disorganized bile acid physiology could result in an altered energy balance. The role of bile acids in maintaining the intestinal barrier function and the luminal environment must too be called to mind, including their capacity to prevent SIBO and bacterial translocation (Hagey and Krasowski, 2013; Karatepete al., 2010). Additionally, bile acids are involved in energy and lipid metabolism, be-

ing capable of lowering triglyceride levels, for example (Trauner et al., 2010). Therefore, the microbiota could, because to effects on bile acid metabolism in the gut lumen, influence signalling pathways involved in energy and lipid metabolism. The consequences of this involvement include the regulation of secondary bile acid metabolism, the inhibition of bile acid synthesis, modifications to lipid peroxidation and the storage of fatty acids in the liver (Sayin et al. 2013).

Insulin resistance

Insulin resistance is crucial in the pathogenesis of the metabolic syndrome, of which NAFLD is considered as the hepatic component. Insulin resistance appears to have a crucial role in the pathogenesis of NAFLD and NASH (Finelli and Tarantino, 2013a). Besides the suggested role of insulin resistance in the development of steatosis, hepatic insulin resistance could promote hepatocyte injury and inflammation (Tarantino et al., 2009). Gut flora and gut derived endotoxemia are considered main factors in developing insulin resistance. The key link is represented by the lipopolysaccharide–toll like receptor 4 (TLR4)–monocyte differentiation antigen CD14 system (Penas-Steinhardt et al., 2012; Ma et al., 2013; Belforte et al., 2013; Krautbauer et al., 2014). Even if this evidence has been largely gleaned from animal models, one study documented elevated plasma levels of lipopolysaccharide among patients with obesity and type 2 diabetes mellitus (Hawkesworth et al., 2013). Confirmation of these findings and elucidation of the role of the microbiota, gut damage and the pathways for translocation of bacterial debris could open new avenues for prevention and treatment of type 2 diabetes, as reported by Hawkesworth et al. (2013). Suppression or modification of SIBO, by leading to reduced proinflammatory cytokine production, results in a fall in fasting insulin concentrations and decreased insulin resistance (Penas-Steinhardt et al., 2012; Rodríguez-

Hernández et al., 2013). Moreover, Carvalho and Saad (2013) suggested that several strategies focusing on modulation of the gut microbiota (antibiotics, probiotics, and prebiotics) are being experimentally employed in metabolic derangement in order to reduce intestinal permeability, increase the production of short chain fatty acids and anorectic gut hormones, and promote insulin sensitivity to counteract the inflammatory status and insulin resistance found in obese individuals. In another study, it hypothesized that ampicillin improve glucose tolerance in mice only if treatment is initiated prior to weaning and that it disappears when treatment is terminated (Rune et al., 2013). The results supported the hypothesis that a "window" exists early in life in which an alteration of the gut microbiota affects glucose tolerance as well as development of gut immunity and that this window may disappear after weaning (Rune et al., 2013).

The gut microbiota has also been implicated, though in a very different manner, in the pathogenesis of type 1 diabetes mellitus and is an exceedingly complex microenvironment that is intimately linked with the immune system, including the regulation of immune responses (Atkinson and Chervonsky, 2012). Murri et al. (2013) hypothesized that type 1 diabetes in humans could also be linked to a specific gut microbiota Their aim was to quantify and evaluate the difference in the composition of gut microbiota between children with type 1 diabetes and healthy children and to determine the possible relationship of the gut microbiota of children with type 1 diabetes with the glycemic level This is the first study showing that type 1 diabetes is associated with compositional changes in gut microbiota The significant differences in the number of Bifidobacterium, Lactobacillus and Clostridium and in the Firmicutes to Bacteroidetes ratio observed between the two groups could be related to the glycemic level in the group with diabetes (Murri et al., 2013). Moreover, the quantity of bacteria essential

to maintain gut integrity was significantly lower in the children with diabetes than the healthy children. Therefore, Murri et al. (2013) suggested that these findings could be useful for developing strategies to control the development of type 1 diabetes by modifying the gut microbiota. There is increasing evidence that environmental factors acting at the intestinal level, with a special regard to the diverse bacterial species that constitute the microbiota, influence the course of autoimmune diseases in tissues outside the intestine both in humans and in preclinical models (Sorini and Falcone, 2013). These observations suggest factors in the modern environment promote pancreatic islet autoimmunity and destruction of insulin-producing beta cells (Penno et al., 2013). The Environmental Determinants of Islet Autoimmunity (ENDIA) Study is investigating candidate environmental exposures and gene-environment interactions that may contribute to the development of islet autoimmunity and type 1 diabetes (Penno et al., 2013). ENDIA evaluated the microbiome, nutrition, body-weight/composition, metabolome-lipidome, insulin resistance, innate and adaptive immune function and viral infections (Penno et al., 2013). Therefore, Penno et al. (2013) suggested that defining gene-environment interactions that initiate and/or promote destruction of the insulin-producing beta cells in early life will inform approaches to primary prevention of type 1 diabetes.

Altered choline metabolism

Diets deficient in both methionine and choline have been consistently associated with the development and progression of hepatic steatosis, and have been indicated that synergistic effects of protein restriction and choline deficiency influence integrated metabolism and hepatic pathology in mice when nutritional fat content is very high, and support the consideration of dietary choline content in ketogenic diet studies in rodents to limit hepatic mitochondrial dysfunction and fat accumulation (Schugar et

al., 2013). Decreased choline intake is significantly associated with increased fibrosis in postmenopausal women with NAFLD (Guerrerio et al., 2012). Wattacheril et al. (2013) suggest that phospholipid zonation may be associated with the presence of an intrahepatic proinflammatory phenotype and thus have broad implications in the etiopathogenesis of.

Enzymes produced by the gut microbiota catalyze the first step in the conversion of dietary choline to dimethylamine and trimethylamine (Craciun and Balskus, 2012). These metabolites (Rezzi et al., 2007) are absorbed through the microvilli and reach the liver via the portal vein (Tang et al., 2013) where trimethylamine is largely cleared by hepatic first-pass metabolism before it enters the systemic circulation. Germfree mice do not excrete trimethylamine, supporting an essential role for the gut microbiota in the conversion of choline to this compound (Bain et al., 2005). Létoffé et al. (2014) showed that exposure to trimethylamine increases the pH of the growth medium of exposed bacteria, resulting in modifications in antibiotic uptake and transient alteration of antibiotic resistance. This study therefore presents a new mechanism by which volatile compounds, during food transformation and fermentation, can affect community behavior and structure in physically separated bacteria, and it illustrates how airborne chemical interactions between bacteria contribute to the development of bacterial communities (Létoffé et al., 2014).

Diet and mutations of the gut microbiota and host metabolism

Modification of gut microbiota and/or its biochemical ability by specific dietary or pharmacological interventions, may conveniently affect host metabolism. However, in humans to date it is unclear, whether the diet-induced effects depend on pre-existent gut microbial composition, in interaction with the host phenotype, whether oral co-administration of specific bacterial species

together with the dietary substrate is required, and which mechanisms are involved. Crucially, it is unknown whether the observations made in rodents can be extrapolated to humans and ultimately harnessed for clinical purposes. In association with the tools to modulate the gut microbiota, prebiotics (i.e. 'non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of the bacteria in the guts') (Gibson et al., 2004), and probiotics (i.e. 'live microorganisms which, when given orally in quantities adequate to allow colonization of the colon, confer a health benefit to the host') (Bertazzoni et al., 2013), are the most important. Supplementation with inulin-type fructooligosaccharides (FOS), stimulated growth of *Bifidobacterium* spp. and in some cases *Lactobacillus* spp. in humans (Dewulf et al., 2013; Bedani et al., 2013; O'Connell Motherway et al., 2013). These groups of bacteria, often administrated as probiotics, were associated with reduction of intestinal endotoxin levels and improvement of mucosal barrier function (Pinzone et al., 2012; Rao and Samak, 2013; Fouhy et al., 2013). The *Bifidobacteria* count at baseline is strictly related to the increased count after treatment, clearly showing that pre-existent composition of the gut microbiota is central to the response of the intervention (Dewulf et al., 2013). Van Bearlen et al. (2009) showed that expression profiles of human mucosa displayed striking differences in modulation of NF-kappaB-dependent pathways, notably after consumption of living Lactobacillus plantarum bacteria in different growth phases. In a randomized, double-blind, placebo-controlled trial, independently of other lifestyle changes, oligofructose supplementation has the potential to promote weight loss and improve glucose regulation in overweight adults (Parnell and Reimer, 2009). Also, Pedersen et al. showed that oligofructose dose-dependently increased peptide YY, decreased pancreatic polypeptide and tended

to decrease ghrelin, but did not significantly affect appetite profile, energy intake, glucose, insulin, or glucagon-like peptide 1 concentrations during appetite study sessions (Pedersen et al., 2013). Pedersen et al. concluded that oligo-fructose supplementation at ≥ 35 g/day increased peptide YY and suppressed pancreatic polypeptide and hunger; however, energy intake did not change significantly (Pedersen et al., 2013). It has demonstrated that a single gene (encoding linoleic acid isomerase) expressed in an intestinal microbe can influence the fatty acid composition of host fat (Rosberg-Cody et al., 2011). Fava et al. (2013) suggested a new evidence from a large-scale dietary intervention study that high carbohydrate diets, irrespective of glycemic index, can modulate human faecal saccharolytic bacteria, including bacteroides and bifidobacteria Conversely, high fat diets reduced bacterial numbers, and in the high saturated fat diet, increased excretion of short-chain fatty acids (SCFAs), which may suggest a compensatory mechanism to eliminate excess dietary energy (Fava et al., 2013). In contrast, supplementation of non-fermentable carbohydrates such as FOS, which lead to an increase in SFCA formation, had beneficial effects on the host metabolic phenotype, including increased satiety, body weight and - fat loss and improvement in insulin sensitivity and glucose tolerance, with several mechanisms involved (Fouhyet al., 2013; Pourghassem Gargari et al., 2013; Schroeder et al., 2013; Whelan, 2013). Of note, butyrate shows an obvious function of anti-obesity, and can alleviate the metabolic stress, maintain the β-cell function and protect them from inflammatory response in pregnant obese mouse without obvious fetus toxicity (Li et al., 2013). Evidence supporting that dietary inulin alone was effective to prevent the development of hepatic steatosis, ameliorate nutritional effects, and alleviate the hepatic change in the expression of hepatic cytochrome P450 (CYP) mRNA, while co-treatment with statin did not have additive or synergistic effects and

statin may cause adverse effects in rats fed the high-fat and high-sucrose diet (Sugatani et al., 2012). Reimer et al. (2012) reported that novel polysaccharide (NPS) PolyGlycopleX (PGX) and Sitagliptin improve several metabolic outcomes in Zucher diabetic fatty rats, but combined, their ability to markedly reduce glycemia suggests they may be a promising dietary/pharmacological co-therapy for type 2 diabetes management. Probably, the SCFA-induced physiological effects on colonic functions might be attributable to the activation of SCFA receptors on epithelial cells in the colon. (Tazoe et al., 2008). However, highly viscous, non-fermentable fibers may limit weight gain and reduce adiposity and non-fermentable fibers, regardless of viscosity, may promote meal termination (Schroeder et al., 2013). Another, fermentable indigestible carbohydrate increases the number of free fatty acid receptor 2 -positive L-cells in the proximal colon (Schroeder et al., 2013). Free fatty acid receptor 2 activation by SCFAs might be an important trigger for produce and release GLP-1 by enteroendocrine L-cells in the lower intestine (Schroeder et al., 2013). Also, FOS in mice increased the number of intestinal bifidobacteria and reduced the impact of high-fat diet-induced endotoxaemia and inflammation (Pourghassem Gargari et al., 2013; Schroeder et al., 2013). Several studies in humans already support interest in FOS in the control of satiety, triglyceridemia, or steatohepatitis (Delzenne et la., 2007). Moran-Ramos et al. (2012) suggested that the potential for diet interventions as a promising strategy for modulating gut hormone responses to food ingestion and, ultimately, preventing or treating metabolic diseases is being emphasized considering that these diseases are currently a public health burden. The link with gut peptides production in humans remains to be proven.

Therefore, we hypothesize that the effects of dietary factors on gut microbiota and host metabolism, particularly in humans, are as yet widely unknown. These may depend on both the dietary intervention and the pre-existent gut microbial composition, in relation to the host phenotype.

GUT MICROFLORA'S COMPOSITION AND NON-DIETARY FACTORS

Gut microflora composition in an individual's colon likely is influenced by a combination of dietary habits and other host- and non-host-associated factors. For example, the exposure of individuals to microbes capable of establishing residence in the gut might depend on geographic location, with large differences expected between individuals living in areas with different levels of drinking water purity and food quality; different levels of hygiene; or with different climates. Other factors that may contribute to the progression of the intestinal microflora include initial colonization after birth, driven by the presence of selective nutrients in the mother's milk; host genetic factors that influence the secretion of substances that facilitate selection for specific bacteria; immune control that favors growth of some groups of bacteria; and random chance that results in a colonization cascade. Another factor that can alter an established microflora is antibiotic treatment. Antibiotics interfere with the existing microflora by selecting in contrast to vulnerable bacteria and, even after treatment, the re-establishment of the full complexity of the microflora might result in a changed composition. Buccigrossi et al. (2013) sustained that a relationship exists between eubiosis and functions and conversely between dysbiosis and dysfunctions or even diseases. Abnormalities in microflora composition may trigger or contribute to specific diseases. This raises the hypothesis to target microflora in order to restore eubiosis through the use of antibiotics, probiotics or nutrients (Buccigrossi et al., 2013).

Differences between physical activity levels might too change gut microflora composition. Even if moderate exercise has

not been shown to reduce transit time through the intestinal tract, elevated activity levels might change other aspects of intestinal physiology and, in this manner, the conditions for microbial growth (Kim, 2012; Cho et al., 2013). Valdés-Ramos et al. (2010) suggest that high-fat diets combined with exercise are able to induce an increase in CD3+ lymphocytes due to increased CD8+ cells and a decrease in B-cells and the authors concluded that explanations and consequences of the effects of diet and exercise on the gut mucosal immunity are still being explored (Valdés-Ramos et al., 2010). Another, it observed substantial taxonomic changes in the microbiome, changes in copies of key genes involved in the metabolism of carbohydrates to short-chain fatty acids, increases in colonic short-chain fatty acid levels, and alterations in the regulation of hepatic metabolism of lipids and cholesterol (Cho et al., 2012). Therefore, Cho et al. (2012) demonstrated the alteration of early-life murine metabolic homeostasis through antibiotic manipulation. For these findings, we hypothesized that as-yet-undiscovered factors, or random chance, too is partly responsible for the establishment and maintenance of the intestinal microbiota.

In a human dietary intervention study reporting beneficial effects of green and black tea drinking on serum lipids (Hartley et al., 2013), Henning et al. (2013) observed that the consumption of both, green tea and black tea, was associated with a significant increase in urinary and serum phenolic acids. Tea polyphenols are metabolized by the colonic microflora yielding phenolic metabolites, which may contribute to the health benefits of tea (Henning et al., 2013). We hypothesize that, at least for short study intervals, the constituted microflora had an overwhelming effect on the flora's final composition, thus indicating the need for a longer follow-up in dietary studies.

Due to substrate availability, water content, and other physiologic conditions, the highest microbial activity is found in the proximal colon (Tannock, 2002; Macfarlane and Macfarlane, 2012). In that regard, although the microflora's composition appears to be affected by factors that are primarily associated with diet (i.e., changes in substrate availability, pH, and reduction potential), it might also be influenced by genetic and other as-yet-undiscovered factors.

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

The progression of simple steatosis to steatohepatitis is essentially an inflammatory rather than a metabolic process; risk factors associated with this change include obesity and a high BMI (Tarantino et al., 2010; Greene et al., 2014; Alkhouri et al., 2014a). Several lines of evidence, detailed below, have suggested that SIBO might play an important part in progression of NAFLD to NASH. Intestinal failure and total parenteral nutrition (TPN) are associated with NAFLD and progression to NASH (Corbin and Zeisel, 2012; Rollins et al., 2013). SIBO, related probably to intestinal hypomotility as well as other factors, such as suppressed secretion of gastric acid and intestinal enzymes and reduced bile flow, has been considered as a causative factor (Corbin and Zeisel, 2012; Rollins et al., 2013).

The use of TPN in the treatment of critically ill patients has been the subject of debate because it has been associated with alterations in intestinal homeostasis (Hodin et al., 2012). Important factors in maintaining intestinal homeostasis are the intestinal microbiota and Paneth cells, which exist in a mutually amendable relationship. Hodin et al. (2012) showed a shift in intestinal microbiota in TPN-fed rats that correlated with changes in Paneth cell lysozyme expression. Further studies that include interventions with microbiota or nutrients that modulate them may yield information on the involvement of the microbiota and Paneth cells in TPN-associated intestinal compromise (Hodin et al., 2012). However, the contribution of the intestinal microbiome to

liver disease goes beyond simple transloca-tion of bacterial products that promote he-patic injury and inflammation (Schnabl and Brenner, 2014). Microbial metabolites pro-duced in a dysbiotic intestinal environment and host factors are equally important in the pathogenesis of liver disease (Schnabl and Brenner, 2014). Therefore, we hypothesize that the combination of liver insult and dis-ruptions in intestinal homeostasis contribute to liver disease.

The increased abundance of alcohol-producing bacteria in NASH microbiomes, elevated blood-ethanol concentration in NASH patients, and the well-established role of alcohol metabolism in oxidative stress and, thus, liver inflammation suggest a role for alcohol-producing microbiota in the pathogenesis of NASH (Zhu et al., 2013). Zhu et al. (2013) postulated that the distinct composition of the gut microbiota among NASH, obese, and healthy controls could offer a target for intervention or a marker for disease. In addition, several ex-perimental studies and clinical trials re-vealed promising effects of probiotics in improving NAFLD; however given the lim-ited experience in this field, generalization of probiotics as treatment of NAFLD needs substantiation through more trials with a larger sample sizes and with longer-term follow up (Kelishadi et al., 2013).

Younossi et al. (2014) suggested that NASH associated with metabolic syndrome can progress advanced fibrosis and cirrho-sis. Weight loss and lifestyle modification have been shown to improve NASH. Other medications used for weight loss and meta-bolic syndrome have been evaluated, such as orlistat, metformin and thiazolidinedi-ones, as reported by Younossi et al. (Younossi et al., 2014). Alternative regi-mens using ursodeoxycholic acid, statins and probiotics as well as bariatric surgery have been evaluated, but have not been rec-ommended as first-line treatment for NASH (Younossi et al., 2014). Vitamin E for NASH patients without diabetes seems to be promising (Younossi et al., 2014). The

lack of effective treatment for NASH sug-gests the heterogeneity of patients present-ing with the NASH phenotype (Younossi et al., 2014). The best treatment strategy for these patients may be to identify their path-ogenic target and develop personalised treatment protocols (Younossi et al., 2014). Shanab et al. showed that NASH patients have a higher prevalence of SIBO which is associated with enhanced expression of TLR-4 and release of IL-8 (Shanab et al., 2011). SIBO may have an important role in NASH through interactions with TLR-4 and induction of the pro-inflammatory cytokine, IL-8 (Shanab et al., 2011). It showed that probiotic combination with metformin im-proves liver aminotransferases better than metformin alone in patients with NASH (Shavakhi et al., 2013).

Nevertheless, NASH recurs immediate-ly after liver transplantation unless the jeju-noileal bypass is removed (Charlton, 2013). However, Wu et al. (2008) suggested that SIBO may decrease small intestinal move-ment in NASH rats. Another, SIBO may be an important pathogenesis of NASH and treatment with cidomycin by mouth can al-leviate the severity of NASH (Wu et al., 2008). In addition, gut flora and bacterial translocation play important roles in the pathogenesis of chronic liver disease, in-cluding cirrhosis and its complications (Ilan, 2012). Intestinal bacterial overgrowth and increased bacterial translocation of gut flora from the intestinal lumen predispose patients to bacterial infections, major com-plications and also play a role in the patho-genesis of chronic liver disorders (Ilan, 2012). A better understanding of the cell-specific recognition and intracellular signal-ing events involved in sensing gut-derived microbes will help in the development of means to achieve an optimal balance in the gut-liver axis and ameliorate liver diseases (Ilan, 2012). These may suggest new targets for potential therapeutic interventions for the treatment of NASH (Ilan, 2012). Both obesity and diabetes, key factors in NASH progression, are also associated with intes-

tinal dysmotility (Stenkamp-Strahm et al., 2013), which could potentially lead to SIBO (Bures et al., 2010; Jacobs et al., 2013; Mushref and Srinivasan, 2013). Ghrelin, a gastric hormone that regulates food intake, also exerts prokinetic effects (Strasser, 2012; Queipo-Ortuño et al., 2013). Patients with NASH show low ghrelin levels (Gonciarz et al., 2013; Machado et al., 2012), which could lead to reduced gut motility and encourage retrograde colonization of the small intestine by colonic bacteria and, probably, the progression of SIBO.

Rana et al. (2014) showed that increase in cytokines and decrease in anti-oxidants in ulcerative colitis patients would have resulted in oxidative stress causing delayed gastrointestinal motility leading to SIBO.

Miele et al. (2009) suggested that NAFLD in humans is associated with increased gut permeability and that this abnormality is related to the increased prevalence of SIBO in these patients. The increased permeability appears to be caused by disruption of intercellular tight junctions in the intestine, and it may play an important role in the pathogenesis of hepatic fat deposition (Miele et al., 2009). Disruption of tight junctions between intestinal epithelial cells by bacterial toxins or other inflammatory mediators leads to translocation of intraluminal contents (and, notably, bacterial endotoxins) into the systemic circulation.

Sachdev and Pimentel (2013) suggested that quantitative culture of small bowel contents and a variety of indirect tests have been used over the years in an attempt to facilitate the diagnosis of SIBO. The indirect tests include breath tests and biochemical tests based on bacterial metabolism of a variety of substrates. Infact, Rana and Bhardwaj (2008) suggested that SIBO can be diagnosed by: 1) culture of jejunum aspirate for bacterial counts, 2) 14C-D-xylose breath testing, 3) non-invasive hydrogen breath testing using glucose or lactulose or 4) 14C-glycocholic acid breath testing. Ac-

tually, there is no single valid test for SIBO, and the accuracy of all current tests remains limited due to the failure of culture to be a gold standard and the lack of standardization of the normal bowel flora in the small intestine (Sachdev and Pimentel, 2013). Interestingly, in morbidly obese patients, bacterial overgrowth prevalence is higher than in healthy subjects and is associated with severe hepatic steatosis (Sabaté et al., 2008). Therefore, the ideal approach to treat SIBO is to treat the underlying disease, eradicate overgrowth, and address nutritional deficiencies that may be associated with the development of SIBO (Sachdev and Pimentel, 2013).

THE GUT MICROBIOTA AND HEPATOTOXIC EFFECTS

The gut microflora has been identified to have possible hepatotoxic effects for numerous years. Indeed, the intestinal microbiota produces a number of probably hepatotoxic compounds, such as ammonia, ethanol, acetaldehyde, phenols and benzodiazepines, which must be consequently metabolized in the liver. Bacterial endotoxins reaching the liver through the portal circulation activate the hepatic Kupffer cells and stimulate their production of nitric oxide and cytokines. Altered intestinal permeability might ease the delivery of these hepatotoxic factors to the liver. Bacterial endotoxin, such as lipopolysaccharide (LPS), plays an important role in the pathogenesis of NAFLD (Fukunishi et al., 2014). In fact, Fukunishi et al. (2014) suggest that LPS may accelerate the progression of hepatic steatosis. In association with the numerous bacterial products, lipopolysaccharide and ethanol appear to be the most important factors in NAFLD pathogenesis.

Lipopolysaccharide

Lipopolysaccharide (LPS), the active component of endotoxin, binds to lipopolysaccharide binding protein (LBP), CD14, TLR4 and lymphocyte antigen 96, among other receptors. Roh and Seki (2013) sug-

gested that gut microflora-derived bacterial products (i.e. LPS) and endogenous substances (i.e. high-mobility group protein B1 [HMGB1], free fatty acids) released from damaged cells activate hepatic TLRs that contribute to the development of alcoholic and NASH and liver fibrosis. The crucial role of TLR4, a receptor for LPS, has been implicated in the development of alcoholic steatohepatitis, NASH, liver fibrosis, and hepatocellular carcinoma (Roh and Seki, 2013).

In fact, LPS binds to LBP and the LBP–LPS complex binds to CD14 on Kupffer cells. Then TLR associates with CD14 on the cell surface, triggering an essential intracellular inflammatory cascade, including stress-activated and mitogen-activated protein kinases, c-Jun N-terminal kinase (JNK), p38 and the nuclear factor κB (NFκB) pathway. Activation of Inhibitor of NFκB kinase β subunit kinase (IKK) leads to the phosphorylation and complete degradation of IKK-β, an NFκB inhibitor. NFκB translocates to the nucleus, where it binds to the promoter region of a number of target genes involved in the inflammatory pathway, such as TNF and IL-1β.

Metabolic effects

Endogenous lipopolysaccharide is a complex of polysaccharide components and lipids. The lipid moiety, termed lipid a, is thought to be relevant to the induction of metabolic effects. In mice, lipopolysaccharide infusion resulted in increased fasting levels of glucose and insulin, as well as weight gain; the effects of this treatment on total body fat, steatosis and adipose tissue were similar to those induced by a high-fat diet. In parallel with these changes, the numbers of macrophages in adipose tissue and levels of inflammatory markers and hepatic triglycerides increased. In addition, insulin sensitivity in the liver (but not in other body tissues) was modified in lipopolysaccharide infused mice. Visceral and subcutaneous fat deposition was likewise increased in both the high-fat diet and lipo-polysaccharide infused groups of animals (Krautbauer et al., 2014).

Moreover, fat ingestion elevates the effectiveness of translocation of intestinal bacterial LPS (Lee, 2013). A high-fat diet produces a considerable quantity of lipoprotein containing chylomicrons, which promote LPS translocation to extraintestinal tissues (Demignot et al., 2014). For individuals on a high-fat diet, therefore, a primary factor in the induction of metabolic diseases could be activation of an inflammatory cascade, induced by lipopolysaccharide binding to the complex of lymphocyte antigen 96, CD14 and TRL4 on the surface of immune cells (Racioppi et al., 2012). Another, Racioppi et al. (2012) sustained that calcium/calmodulin-dependent kinase kinase 2 (CaMKK2) plays a key role in regulating food intake and energy expenditure at least in part by its actions in hypothalamic neurons.

Lipopolysaccharide can stimulate monocytes and macrophages to produce the pro-inflammatory cytokines TNF, IL1 and IL6 (Li et al., 2014). Accordingly, several studies have reported high levels of proinflammatory cytokines, notably TNF, in obese individuals (Miele et al., 2009; Zhong et al., 2013; Gonzalez-Quintela et al., 2013; Zunino et al., 2013). TNF can induce insulin resistance by dual effects on insulin sensitive tissues, and this cytokine rapidly abolishes insulin receptor signalling in adipocytes, hepatocytes and skeletal muscle cells in tissue culture (Lorenzo et al., 2008; Di Renzo et al., 2013; Carstensen et al., 2014). Furthermore, TNF-α in male Wistar rats models showed improved glucose and insulin homeostasis (Ahmed et al., 2014). CD14, which acts as a lipopolysaccharide co-receptor along with lymphocyte antigen 96 and TLR4, might be the main molecule mediating insulin resistance and, hence, the occurrence of obesity and diabetes. Obese rodents lacking CD14 were protected from obesity, diabetes, the development of steatosis and visceral fat mass accumulation af-

ter lipopolysaccharide administration (Krautbauer et al., 2014).

Proinflammatory effects

In a murine model with NAFLD, hepatic fat accumulation induces the liver to further grave injury by hepatotoxins and/or infectious agents, leading to NASH and the eventual progression of cirrhosis (Vansaun et al., 2013). Shen et al. (2005) reported that addition of leptin to normal rats increased LPS-induced hepatic TNF-alpha production in vivo and leptin receptor-deficient Zucker rats showed reduced hepatic TNF-alpha production on addition of LPS in vivo. These findings indicate that P38 and JNK pathways are involved in the signal transduction of leptin enhancement of LPS-induced TNF-alpha production (Shen et al., 2005). Furthermore, Imajo et al. demonstrated that up-regulation of CD14 by leptin-mediated signaling is critical to hyperreactivity against endotoxin during NASH progression (Imajo et al., 2012). Up-regulation of CD14 in Kupffer cells and hyperreactivity against low-dose LPS were observed in high-fat diet (HFD)-induced steatosis mice, but not chow-fed-control mice (Imajo et al., 2012). Hyperresponsivity against low-dose LPS led to accelerated NASH progression, including liver inflammation and fibrosis. Administering leptin in chow-fed mice caused increased hepatic expression of CD14 via STAT3 signaling, resulting in hyperreactivity against low-dose LPS without steatosis. In contrast, a marked decrease in hepatic CD14 expression was observed in leptin-deficient ob/ob mice, despite severe steatosis (Imajo et al., 2012).

Lipopolysaccharide induced production of cytokines is initiated by binding of lipopolysaccharide to LBP, followed by the attachment of this complex to CD14 on Kupffer cells. TLR4 associates with CD14 on the cell surface to initiate lipopolysaccharide induced signal transduction - notably, activation of nuclear factor Kb (NFκB) and the subsequent production of proinflammatory cytokines, such as TNF and cyclooxygenase 2 (Imajo et al., 2012; Ling et al., 2014). Activation of TLR4 by lipopolysaccharide triggers an essential intracellular inflammatory cascade, including stress-activated and mitogen-activated protein kinases, c-Jun-N-terminal kinase, p38 and the nFκB pathway. Activation of inhibitor of NFκB kinase subunit β (IKKβ) kinase leads to the phosphorylation and complete degradation of IKKβ, an NFκB inhibitor. Removal of IKKβ allows NFκB to translocate to the nucleus, where it binds to the promoter region of a number of target genes involved in the inflammatory pathway, such as TNF and IL-1β (Huang and Hung, 2013). Thus, NFκB might be a key factor in the induction of pro-inflammatory cytokines.

Evidence, mostly from animal models, shows that this pathway is activated in the presence of NASH. Ruiz et al. (2007) showed that NAFLD patients have elevated plasma levels of LPS-binding and they are further increased in patients with NASH. This increase is related to a rise in TNF-alpha gene expression in the hepatic tissue which supports a role for endotoxemia in the development of steatohepatitis in obese patients, as reported by Ruiz et al. (2007).

Stanković et al. (2014) suggested that methionine-choline deficient (MCD) diet duration necessary for development of NAFLD and the dynamic of lipid profile and fatty acids are not completely established. Therefore, in their study examined dynamics and association between liver free fatty acids, serum lipid profile and liver morphological changes on MCD diet-induced NAFLD in mice. Stanković et al. (2014) concluded that supplementation with n-3 polyunsaturated acid, especially in the initial stage of fatty liver disease, may potentially have preventive effects and alleviate development of NAFLD/NASH and may also potentially reduce cardiovascular risk by moderating dyslipidemia (Stanković et al., 2014).

Some studies have suggested that bacterial overgrowth and endotoxemia along

with its receptor, TLR-4, play a role in the pathogenesis of NAFLD. Kiziltas et al. (2014) reported that as the first-time-in-humans controlled study related to investigation of TLR4 gene polymorphism in NAFLD, their findings contribute to the available data that TLR-4 signaling is pivotal for the pathogenesis of NASH and indicate that the TLR4 codon 299 heterozygous gene mutation (Asp299Gly) in humans may have a preventive role against the genesis of NAFLD.

Inflammatory cytokines, such as TNF-α and IFN-γ, induce, as reported by Kawaratani et al. (2013), liver injury in the rat model of NASH. Another, hepatoprotective cytokines, such as IL-6, and anti-inflammatory cytokines, such as IL-10, are also associated with NASH (Kawaratani et al., 2013). Besides, IL-6 improves NASH via activation of the signal transducer and activator of transcription 3 (STAT3) and the subsequent induction of a variety of hepatoprotective genes in hepatocytes (Kawaratani et al., 2013). IL-10 inhibits alcoholic liver inflammation via activation of STAT3 in Kupffer cells and the subsequent inhibition of liver inflammation (Kawaratani et al., 2013). Alcohol consumption promotes liver inflammation by increasing translocation of gut-derived endotoxins to the portal circulation and activating Kupffer cells through the LPS/TLR 4 pathways. Another, oxidative stress and microflora products are also associated with NASH (Kawaratani et al., 2013). Therefore, interactions between pro- and anti-inflammatory cytokines and other cytokines and chemokines are likely to play important roles in the development of NASH (Kawaratani et al., 2013).

Hepatic stellate cells (HSCs) could play a main role in generating the liver inflammatory cascade associated with endotoxemia (Harvey et al., 2013; Stewart et al., 2014).

HSCs are the major cell type involved in liver fibrosis. Lipopolysaccharide (LPS)-mediated signaling through TLR4 in HSCs has been identified as a key event in liver fibrosis, and as the molecular link between inflammation and liver fibrosis (Zhao et al., 2014). Therefore, Zhao et al. investigated the effects of caffeic acid phenethyl ester (CAPE), one of the main medicinal components of propolis, on the pro-inflammatory and fibrogenic phenotypes of LPS-stimulated HSCs (Zhao et al., 2014). HSCs from rats were isolated and cultured in Dulbecco's modified Eagle's medium (DMEM) (Zhao et al., 2014). Following treatment with LPS, HSCs showed a strong pro-inflammatory phenotype with an up regulation of pro-inflammatory mediators, and a fibrogenic phenotype with enhanced collagen synthesis, mediated by transforming growth factor-β1 (TGF-β1) (Zhao et al., 2014). CAPE significantly and dose-dependently reduced LPS-induced nitrite production, as well as the transcription and protein synthesis of monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6) and inducible nitric oxide synthase (iNOS), as determined by quantitative reverse transcription-polymerase chain reaction (qRT-PCR), western blotting and enzyme-linked immunosorbent assays (ELISA) (Zhao et al., 2014). CAPE further reduced the TGF-β1-induced transcription and translation (protein synthesis) of the gene coding for collagen type I α1 (col1A1), in LPS-stimulated HSCs (Zhao et al., 2014). Following LPS stimulation, the phosphorylation of the nuclear factor-κB (NF-κB) inhibitor IκBα and consequently, the nuclear translocation of NF-κB, were markedly increased in the HSCs, and these changes were reversed by pre-treatment with CAPE (Zhao et al., 2014). Zhao et al. (2014) concluded that CAPE attenuates the pro-inflammatory phenotype of LPS-stimulated HSCs, as well as the LPS-induced sensitization of HSCs to fibrogenic cytokines by inhibiting NF-κB signaling. These results provide new insight into the treatment of hepatic fibrosis through regulation of the TLR4 signaling pathway (Zhao et al., 2014). Thus, HSCs play an important role both in endotoxin-induced acute

hepatocyte injury, with TNF-α and endothelin-1 as important mediators of these effects (Stewart et al., 2014).

Ethanol

Acetaldehyde and acetate are two major metabolites of ethanol. Ethanol can increase production of acetate via inhibition of the tricarboxylic acid cycle. In turn, acetate is a substrate for fatty acid synthesis (Sato et al., 2014). Acetaldehyde and its metabolites might lead to the formation of reactive oxygen species, which increase oxidative stress and, ultimately, induce liver injury (Tarantino et al., 2014).

Ye et al. (2013) investigated the role of Cytochrome P4502E1 in sensitizing Kupffer cells to LPS-mediated inflammation after ethanol induction. As reported by Ye et al. (2013), in cultured Kupffer cell, using chlormethiazole as inhibitor, ethanol-induced CYP2E1 overexpression was proved to contribute to the sensitization of Kupffer cells to LPS stimuli, with amplification of ROS production and activation of NF-κB, resulting in increased TNF-α production.

Alkhouri et al. (2014b) showed that exhaled breath analysis is a promising non invasive method to detect fatty liver in children. Therefore, isoprene, acetone, trimethylamine, acetaldehyde, and pentane are novel biomarkers that may help to gain insight into pathophysiological processes leading to the development of NAFLD (Alkhouri et al., 2014b). Treating these animals with probiotics to modify the gut microbiota improved NAFLD histology and decreased serum levels of liver enzymes (Penas-Steinhardt et al., 2012). Zhu et al. (2013) showed that the increased abundance of alcohol-producing bacteria in NASH microbiomes, elevated blood-ethanol concentration in NASH patients, and the well-established role of alcohol metabolism in oxidative stress and, consequently, liver inflammation suggest a role for alcohol-producing microbiota in the pathogenesis of NASH. Ethanol is partly responsible for the physiological and morphological modifications in the intestinal barrier associated with SIBO, and thus enhances the passage of endotoxins from the gut lumen into the portal blood (Cariello et al., 2010). Nair et al. (2001) suggested that higher breath ethanol concentrations are observed in obese subjects than in leaner ones (Nair et al., 2001). It is possible that intestinally derived ethanol may contribute to the pathogenesis of NASH.

PROBIOTICS AND PREBIOTICS

In vitro studies, as reported by Druart et al. (2014), have suggested that isolated gut bacteria are able to metabolize PUFA into CLA (conjugated linoleic acids) and CLnA (conjugated linolenic acids). However, the bioavailability of fatty acid metabolites produced in vivo by the gut microbes remains to be studied. Druart et al. (2014) concluded that the accumulation of the main metabolites (CLA cis-9,trans-11-18:2 and CLnA cis-9, trans-11, cis-15-18:3) in the caecal tissue was not associated with their increase in the plasma, therefore suggesting that, if endogenously produced CLA and CLnA have any biological role in host metabolism regulation, their effect would be confined at the intestinal level, where the microbiota is abundant (Druart et al., 2014). The effects of administering prebiotics have illustrated the ability of the gut microbiota to affect host metabolism by both reducing energy intake and protecting the host from weight gain; the latter effect might be mediated by altered release of gut peptides involved in appetite and weight control (Pyra et al., 2012; Koleva et al., 2012; Everard et al., 2013; Bomhof et al., 2014; Dewulf et al., 2013; Closa-Monasterolo et al., 2013).

Rauch and Lynch (2012) suggested that modulating microbial exposure through probiotic supplementation represents a long-held strategy towards ameliorating disease via intestinal microbial community restructuring. Therefore, this field has experienced somewhat of resurgence over the past few years, primarily due to the expo-

nential increase in human microbiome studies and a growing appreciation of our dependence on resident microbiota to modulate human health (Rauch and Lynch, 2012). Wang et al. (2013b) reported that the therapeutic effects of probiotic treatment in alcoholic liver disease have been studied in both patients and experimental animal models. Although the precise mechanisms of the pathogenesis of alcoholic liver disease are not fully understood, gut-derived endotoxin has been postulated to play a crucial role in hepatic inflammation (Wang et al., 2013b). Previous studies have demonstrated that probiotic therapy reduces circulating endotoxin derived from intestinal gram-negative bacteria in alcoholic liver disease. Wang et al. (2013b) concluded that probiotic Lactobacillus rhamnosus GG (LGG) treatment reduced alcohol-induced hepatic inflammation by attenuation of TNFα production via inhibition of TLR4- and TLR5-mediated endotoxin activation (Wang et al., 2013b). Another, early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut seems to be a potentially valuable complement to the routine treatment protocol of severe acute pancreatitis, as reported by Plaudis et al. (Plaudis et al., 2012). Therefore, the ethanol-induced pathogenic changes in the microbiome and the liver were prevented by LGG supplementation (Bull-Otterson et al., 2013). Overall, significant alterations in the gut microbiome over time occur in response to chronic alcohol exposure and correspond to increases in intestinal barrier dysfunction and development of alcoholic liver disease (Bull-Otterson et al., 2013). Furthermore, the altered bacterial communities of the gut may serve as significant therapeutic target for the prevention/treatment of chronic alcohol intake induced intestinal barrier dysfunction and liver disease (Bull-Otterson et al., 2013). Dewulf et al showed that inulin-type fructans, which promote gut fermentation, paradoxically counteract GPR43 (a G protein-coupled receptor, potential link between gut fermentation processes and white

adipose tissue development) overexpression induced in the adipose tissue by an high-fat diet, a phenomenon that correlates with a beneficial effect on adiposity and with potential decrease in PPARγ-activated processes (Dewulf et al., 2011).

Probiotics alter the intestinal microbiota with non-urease-producing organisms that reduce production of ammonia (Lunia et al., 2013). In a prospective, randomized controlled trial conducted by Lunia et al., probiotics were found to be effective in preventing hepatic encephalopathy in patients with cirrhosis (Lunia et al., 2013).

Lactulose promotes equol production and changes the microbial community during in vitro fermentation of daidzein by fecal inocula of sows (Zheng et al., 2014). Equol has higher biological effects than other isoflavones. However, only about 30-50 % of humans possess a microbiota capable of producing equol from dietary daidzein. In recent years, interest has grown in dietary applications to improve equol production in human and other animals. Zheng et al. (2014) showed that lactulose was used as a potential equol-promoting prebiotic in vitro. The effect of lactulose on transformation of daidzein into equol by sows' fecal microbiota was investigated (Zheng et al., 2014). Results showed that lactulose treatment improved bacteria growth parameters, changing the kinetics of fermentation in vitro. Lactulose significantly increased total gas production (Zheng et al., 2014). Furthermore, lactulose altered the microflora composition, increased equol production associated with a reduction in the population of methanogen and increased the sulfate-reducing bacteria population during 24 h of incubation. Zheng et al. (2014) reported for the first time that in a certain condition (sealing or high pressure), via a dihydrodaidzein pathway equol might be able to reform to daidzein by further metabolism using lactulose as a substrate. Zheng et al. (2014), in this study, proposed that "hydrogen-producing prebiotic" might be a novel way to promote equol production in vivo or

in vitro (Zheng et al., 2014). Finally, experimental models, as reported by Imajo et al. (2014), have highlighted several mechanisms connecting microbiota to the development of liver dysfunction in NASH such as increased energy harvesting from the diet, small intestine bacterial overgrowth, modulation of the intestinal barrier by glucagon-like peptide-2 secretions, activation of innate immunity through the lipopolysaccharide-CD14 axis caused by obesity-induced leptin, periodontitis, and sterile inflammation. The manipulation of microbiota through probiotics, prebiotics, antibiotics, and periodontitis treatment yields encouraging results for the treatment of obesity, diabetes, and NASH, but data in humans is scarce (Imajo et al., 2014).

Metabolic effects

Tomaro-Duchesneau et al. (2014) indicated that administration of the ferulic acid (a phenolic acid found in foods normally consumed by humans that has demonstrated antioxidant activity, cholesterol-lowering capabilities, and anti-tumorigenic properties) producing L. fermentum NCIMB 5221 has the potential to reduce insulin resistance, hyperinsulinemia, hypercholesterolemia, and other markers involved in the pathogenesis of metabolic syndrome. Certain probiotics, including *Lactobacillus* and *Bifidobacterium* spp., have the capacity to synthesize bile salt hydrolase (Ruiz et al., 2013), a key enzyme in the deconjugation of bile acids. Deconjugated bile acids are less effective in micelle formation and the emulsification of ingested lipids than conjugated bile acids and, therefore, reduce the efficiency of fat absorption (Cirin et al., 2011; Yokota et al., 2012; Hagey and Krasowski, 2013; Cherrington et al., 2013; Chen et al., 2013). Through cholesterol-lowering effects, *Lactobacillus* and *Bifidobacterium* spp. can ameliorate dyslipidemia (Banjoko et al., 2012; Wang et al., 2013a). In obese and/or dyslipidemic patients, administration of the LAB probiotic mixture ameliorated the levels of total cholesterol

and LDL-cholesterol (Jones et al., 2013; Rai et al., 2013; Tuohy et al., 2014). The effects Lactobacillus reuteri GMNL-263 (Lr263), a new probiotic strain developed by Hsieh's laboratory, on insulin resistance and the development of hepatic steatosis in high-fructose fed rats were explored (Hsieh et al., 2013). The levels of serum glucose, insulin, leptin, C-peptide, glycated hemoglobin, GLP-1, liver injury markers, lipid profile in serum and liver were significantly increased in high-fructose-fed rats (Hsieh et al., 2013). However, after Lr263 administration, the elevation of these parameters was significantly suppressed (Hsieh et al., 2013). Therefore, the Hsieh's study provided evidences clarifying the effectiveness of Lr263 on reducing insulin resistance as well as hepatic steatosis formation in high-fructose-fed rats and suggested that Lr263 may be a promising therapeutic agent in treating type 2 diabetes (Hsieh et al., 2013). Experimental evidence revealed that obesity-associated NAFLD is linked to changes in intestinal permeability and translocation of bacterial products to the liver (Ritze et al., 2014). Actually, no reliable therapy is available except for weight reduction. Ritze et al. (2014) examined the possible effect of the probiotic bacterial strain Lactobacillus rhamnosus GG (LGG) as protective agent against experimental NAFLD in a mouse model. LGG increased beneficial bacteria in the distal small intestine. Moreover, LGG reduced duodenal IκB protein levels and restored the duodenal tight junction protein concentration (Ritze et al., 2014). Ritze et al. showed for the first time that LGG protects mice from NAFLD induced by a high-fructose diet. The underlying mechanisms of protection likely involve an increase of beneficial bacteria, restoration of gut barrier function and subsequent attenuation of liver inflammation and steatosis (Ritze et al., 2014). Rosberg-Cody et al. (2011) demonstrated that a single gene (encoding linoleic acid isomerase) expressed in an intestinal microbe can influence the fatty acid composition of host fat.

Anti-inflammatory effects

Probiotics have several anti-inflammatory effects (Table 1) that could contribute to clinical benefit in NAFLD (Ritze et al., 2014): competition with and displacement of pathogenic strains in SIBO, particularly those with limited adherence ability *in vitro* (Abedi et al., 2013); alteration of inflammatory pathways produced by intestinal bacterial overgrowth via alteration of cytokine signalling (Audy et al., 2012); amelioration of intestinal barrier function through modulation of cytoskeletal and tight-junction proteins (Miyauchi et al., 2013; Noda et al., 2013); enhancement of the integrity of the intestinal epithelium by providing essential nutrients, especially in the form of medium-chain fatty acids that inhibit apoptosis (Wen et al., 2012); direct inhibition of the production of pro-inflammatory mediators, such as TNF and induction of anti-inflammatory responses in intestinal-epithelial-cell–leukocyte co-cultures (Trapecar et al., 2014); and stimulation of IgA release (Ashraf and Shah, 2014).

In conventional culture there was no Escherichia Coli bacterial translocation in control animals (Eizaguirre et al., 2011). Polymerase chain reaction detected Escherichia Coli bacterial translocation showing higher sensitivity (Eizaguirre et al., 2011). Administration of *Lactobacillus johnsonii* La1, without addition to antioxidants, not reduced bacterial translocation and not attenuated endotoxemia in a rat model of cirrhosis (Soriano et al., 2012). Furthermore, mouse models of acute hepatitis have too showed reductions in the incidence of bacterial translocation and hepatic injury after the administration of several strains of Lactobacillus and Bifidobacterium (Osman et al., 2007; Ahrne and Hagslat, 2011).

FUTURE DIRECTIONS

The importance of gut–liver interactions is also accentuated by the role of the intestinal microbiota in NAFLD. The gut microbiota and SIBO, in particular, are now considered to be crucial factors in the patho-

Table 1: Probiotics and clinical benefit in NAFLD

Metabolic effects
• Reduction availability of calories from indigestible carbohydrates
• Enhancement insulin sensitivity
• Modulation intraluminal bile salt metabolism
• Lower cholesterol
• Production conjugated linoleic acid
• Reduction hepatic fatty acid oxidation
Anti-inflammatory effects
• Competition with and displacement pathogenic strains in small intestinal bacterial overgrowth
• Antibacterial effects mediated by bacteriocins
• Modulation inflammatory pathways induced by bacteria involved in intestinal bacterial overgrowth
• Amelioration intestinal barrier function
• Enhancement integrity of the intestinal epithelium
• Direct inhibition of the production of pro-inflammatory mediators and induction anti-inflammatory responses
• Stimulation release of immunoglobulin A

genesis of NAFLD. Actually, evidence has been widely derived from a variety of animal models; the definition and diagnosis of SIBO in man continues to present a substantial challenge.

Several bacterial components and products have been implicated in the pathogenesis of NAFLD and NASH; in animal models the role of lipopolysaccharide, through its capacity to regulate metabolic processes and activate proinflammatory cytokine production, has been particularly prominent.

Since it is clear, from everything that has been described above, the possible important role of gut derived microbial factors in the development and/or progression of NAFLD, a logical proposition is that modi-

fying the microbiota might have a beneficial effect on this pathological condition.

Complications of liver disease could probably be reduced by altering the microbiota either qualitatively or quantitatively. For example, alteration of the gut microbiota by prebiotics or probiotics might be an important therapeutic strategy in the treatment of NAFLD.

To understand the impact of gut microbes on human health and well-being it is crucial to assess their genetic potential (Qin et al., 2010). The gene set, approximately 150 times larger than the human gene complement, contains an overwhelming majority of the prevalent (more frequent) microbial genes of the cohort and probably includes a large proportion of the prevalent human intestinal microbial genes (Qin et al., 2010).

Several issues remain to be determined: the exact prevalence of SIBO (defined using modern molecular techniques) in NAFLD and NASH, whether the translocation of bacterial products, such as LPs, across the gut wall is significant to these disorders in man and whether tailored interventions (with probiotics, prebiotics, antibiotics, or some combinations thereof) will exert meaningful benefits.

Alcohol consumption increases the SIBO and intestinal permeability of endotoxin (Abhilash et al., 2014). The endotoxin mediated inflammatory signaling plays a major role in alcoholic liver fibrosis (Abhilash et al., 2014). The possible mechanism may be the inhibitory effect of acid ascorbic on SIBO, intestinal barrier defect and IKKβ, which decreased the activation of NF-κB and synthesis of cytokines, as reported by Abhilash (Abhilash et al., 2014). SIBO is also responsible for endotoxemia, systemic inflammation, and its consequences including obesity and NAFLD (Duseja and Chawla, 2014). Relationship between gut microbiota and NAFLD is also dependent on altered choline and bile acid metabolism and endogenous alcohol production by gut bacteria (Duseja and Chawla, 2014). Further evidence linking gut microbiota

with obesity and NAFLD comes from studies showing usefulness of probiotics in animals and patients with NAFLD, as suggested by Duseja et al. (Duseja and Chawla, 2014).

Diet and nutritional status are among the most important, modifiable determinants of human health. The nutritional value of food is determined partially by a person's gut microbial community (microbiota) and its component genes (microbiome). Separating the interactions between diet, the structure and operations of the gut microbiota, and nutrient and energy harvest is confounded by changes in human environmental exposures, microbial ecology and genotype.

The human gut microbiota and microbial influences on lipid and glucose metabolism, satiety, and chronic low-grade inflammation are known to be involved in metabolic syndrome (Remely et al., 2014). Fermentation end products, especially short chain fatty acids, are believed to engage the epigenetic regulation of inflammatory reactions via free fatty acid receptor and other short chain fatty acid receptors. Remely et al. (2014) suggested that a different composition of gut microbiota in obesity and type 2 diabetes affect the epigenetic regulation of genes. Interactions between the microbiota and epigenetic regulation may involve not only short chain fatty acids binding to free fatty acid receptor. Therefore dietary interventions influencing microbial composition may be considered as an option in the engagement against metabolic syndrome (Remely et al., 2014).

We hypothesized that each step in the process to ultimately bring gut microbiota manipulation to the clinic, in particular to harness its potential for the prevention and treatment of dysmetabolic disorders, needs to be a small, careful and well-controlled one, to be taken in the setting of expert multidisciplinary collaborations (Karlsson et al., 2013). The latter can only be answered by appropriately powered, randomized, controlled clinical trials. Further stud-

ies are required to investigate the human clinical potential of the probiotic formulation in affecting the markers and pathogenesis of metabolic syndrome (Tomaro-Duchesneau et al., 2014), or associated morbidities, according to recent findings showing that modulation of gut microbiota by probiotics has beneficial effects on brain activity in stress conditions, displays anxiolytic-like activity and reduces apoptosis in the lymbic system in animal models of depression (Ait-Belgnaoui et al., 2013). This long-distance effect of probiotics opens up a new field of research mainly at the light of the possible impact on the unbalance of apoptosis-antiapoptosis process , key mechanism inducing NAFLD/NASH (Tarantino et al., 2011).

The main approach to obesity is to unravel the mechanisms involved in nutrient absorption and then the role of gut flora. In conditions of over-nutrition, cells must cope with a multitude of extracellular signals generated by changes in nutrient load, hormonal milieu, adverse cytokine/adipokine profile, and apoptosis/anti-apoptosis processes. To date studies have demonstrate that among all nutrients, lipids and carbohydrates play a major regulatory role in the gene transcription of glycolytic and lipogenic enzymes (epigenetics), insulin, and adipokines. These nutrients mainly exert their effects through the gene expression of sterol responsive binding protein 1 and 2 (SREBP) and the mammalian target of rapamycin (mTOR) (Tarantino and Capone, 2013).

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