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# The gut microbiota: A new target in the management of alcohol dependence?

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ABSTRACT

The gastrointestinal tract is the natural habitat for a huge community of microorganisms, comprising bacteria, viruses, fungi and yeast. This microbial ecosystem codevelops with the host throughout life and is subject to a complex interplay that depends on multiple factors including host genetics, nutrition, life-style, stress, diseases and antibiotics use. The gut microbiota, that refers to intestinal bacteria, has profound influence on the host immune system, metabolism and nervous system. Indeed, intestinal bacteria supply the host with essential nutrients such as vitamins, metabolize bile acids and undigested compounds, defend against pathogen invasion, participate to the development of the intestinal architecture and the intestinal immune system and play an important role in the maintenance of the gut barrier function. More recently, the gut microbiota has been shown to influence brain functions, such as myelin synthesis, the blood-brain barrier permeability and neuroinflammatory responses but also mood and behavior. The cross-talk between microbes and the host implicates a vast array of signaling pathways that involve many different classes of molecules like metabolites produced by the bacteria from dietary or endogenous sources of carbohydrates and proteins (i.e. short-chain fatty acids (SCFAs), indole), neurotransmitters and inflammatory cytokines. This review will focus on the involvement of the gut microbiota in the pathophysiological aspects of alcohol dependence related to the gut barrier function, liver damage and psychological disturbances. We will also discuss the possibility to create new and realistic humanized animal models of alcohol dependence by the use of fecal transplantation.


## Introduction

The gastrointestinal tract is the natural habitat for a huge community of microorganisms, comprising bacteria, viruses, fungi, and yeast. This microbial ecosystem co-develops with the host throughout life and is subject to a complex interplay that depends on multiple factors, including host genetics, nutrition, life-style, stress, diseases, and antibiotics use (Nicholson et al., 2012). The gut microbiota, which refers to intestinal bacteria, has profound influence on the host immune system, metabolism, and nervous system (Fung, Olson, & Hsiao, 2017; Nicholson et al., 2012). Indeed, intestinal bacteria supply the host with essential nutrients such as vitamins, metabolize bile acids and undigested compounds, defend against pathogen invasion, participate in the development of the intestinal architecture and the intestinal immune system, and play an important role in the maintenance of the gut barrier function. More recently, the gut microbiota has been shown to influence brain functions, such as myelin synthesis (Hoban et al., 2016), blood-brain barrier permeability (Braniste et al., 2014), and neuroinflammatory responses; the gut microbiota has also been shown to influence mood and behavior (Cryan & Dinan, 2012). The cross-talk between the microbes and the host implicates a vast array of signaling pathways that involve many different classes of molecules, such as metabolites produced by the bacteria from dietary or endogenous sources of carbohydrates and proteins (i.e., short-chain fatty acids [SCFAs], indole), neurotransmitters, and inflammatory cytokines (Cryan & Dinan, 2012; Nicholson et al., 2012). This review will focus on the involvement of the gut microbiota in the

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pathophysiological aspects of alcohol dependence related to the gut barrier function, liver damage, and psychological disturbances. Currently, studies that focused on the alteration of the gut microbiota in alcohol-related diseases and their implications for the body arose from two, still distinct fields of research: one developed by hepatologists, which questions the influence of the microbiota on the liver, and another one developed by specialists in alcohol addiction and neuroscience, which questions how the microbiota might influence drinking behavior. In this review, we described the data obtained from these two fields, because all studies are relevant to the entire domain and we also believe that the distinction between these two fields is probably artificial, as the addiction overall could be considered as the result of a gut-liver-brain alteration. Finally, in this review, we will also discuss the possibility to create new and realistic humanized animal models of alcohol dependence by the use of fecal transplantation.

## Effect of alcohol on the gut barrier function

The intestinal mucosal surface is constantly in contact with a vast, diverse, and dynamic microbial community. The intestinal cells must sense and respond appropriately to this enormous microbial load. The gut barrier is a complex system that insures two major defense functions that are physical and immunological: minimizing direct contact between microorganisms and the epithelial cells, and confining penetrant bacteria to intestinal sites, thereby limiting their contact with other host tissues (Hooper, Littman, & Macpherson, 2012). This anatomical containment of intestinal microorganisms is essential to limit inflammation and maintain normal systemic immune cells homeostasis. The intestinal barrier is composed of several components that are described hereafter. First, there is the epithelial barrier where the **enterocytes** are adhered to their adjacent cells due to an apical junctional complex, composed of **tight junctions** (occludin, zonula occludens, and claudins), adherens junctions, and desmosomes. These elements constitute a physical barrier that regulates the paracellular pathways and prevents bacterial translocation (Turner, 2009). Second, there is the **mucus** that forms a protective layer that also limits the penetration of bacteria into host tissues (Johansson et al., 2008). The main constituents of the mucus are the glycoprotein mucins (such as MUC2) produced by the goblet cells. Third, there are the **antimicrobial peptides** that kill or inactivate microorganisms and maintain homeostasis. These natural antibiotics (α- and β-defensins, cathelicidins, lysozyme, angiogenin, phospholipase A2, and C-lectin, such as Reg3γ) are secreted by enterocytes and Paneth cells located at the base of small intestinal crypts and released in the mucus layer (Gallo & Hooper, 2012). Finally, the **gut-associated lymphoid tissue** (GALT), which contains more than 80% of immunoglobulin (Ig)-secreting cells of the entire body (van der Heijden, Stok, & Bianchi, 1987), is also an important component of the gut barrier. Microorganisms that penetrate the intestinal epithelium are phagocytosed and eliminated by macrophages of the lamina propria or engulfed by dendritic cells and carried to the mesenteric lymph nodes. IgA antibodies specific for intestinal bacteria are produced by plasma cells (B lymphocytes), translocate across the epithelium, and bind to luminal bacteria to prevent microbial translocation across the epithelial barrier. Homeostasis in the gut mucosa is also maintained by other lymphocyte types belonging to the GALT, such as $T_H1$ cells that produce interferon (IFN)-γ, $T_H17$ cells that produce IL-17 and IL-22, and $Foxp3^+$ regulatory T cells (Hooper et al., 2012).

In addition, the gut wall contains an autonomous neural network called the enteric nervous system (ENS), composed of $1 \times 10^8$ neurons (Powell, Walker, & Talley, 2017). The ENS controls gut motility and fluid movement and regulates endocrine function. It also directly communicates with mucosal immune cells of the gut barrier, and is in extensive communication with the central nervous system (CNS) via the vagus nerve and the spinal nerves (Powell et al., 2017).

Experimental and clinical studies have demonstrated that alcohol exposure alters the gut barrier function, resulting in increased intestinal permeability and translocation of luminal antigens, mainly bacterial endotoxins such as lipopolysaccharides (LPS), into the portal circulation. The latter can reach the liver where they activate hepatocytes and Kupffer cells, which eventually results in liver damage (Wheeler, 2003). Indeed, patients with alcohol-use disorder (AUD) showed hyperpermeability of the gut mucosa to various molecules such as lactulose/mannitol (Keshavarzian et al., 1999), polyethylene glycol (Parlesak, Schäfer, Schütz, Bode, & Bode, 2000), and $^{51}$Cr-EDTA (Bjarnason, Peters, & Wise, 1984; Leclercq et al., 2012). The mechanisms that could explain the leaky gut in AUD patients are still incompletely understood, but likely implicate the different components of the gut barrier function described above. For instance, *in vitro*, ethanol and its main metabolite acetaldehyde disrupt the epithelial tight junctions and adherence junctions integrity (Elamin et al., 2012; Wang et al., 2014). Alcohol-induced tight junction proteins disassembly has been confirmed in animal studies, and potential mechanisms are described in another review (Zhou & Zhong, 2017). A growing body of evidence has also revealed a deleterious effect of ethanol on mucus and antimicrobial peptide production, as demonstrated by decreased levels of Reg3g (Yan et al., 2011) in duodenal biopsies of patients with alcohol dependence. Intestinal levels of Reg3g were also lower in mice continuously fed with ethanol, and were associated with enhanced bacterial translocation and progression of liver disease (Yan et al., 2011). By contrast, overexpression of Reg3g in intestinal epithelial cells restricts bacterial colonization of mucosal surfaces, reduces bacterial translocation, and protects mice from alcohol-induced steatohepatitis (Wang et al., 2016). The production of mucins was elevated in alcohol-fed rats (Grewal & Mahmood, 2009), and the small intestinal mucus layer of AUD patients was found to be thicker, but more permeable, compared to healthy subjects (Hartmann et al., 2013). Knockdown of MUC2 resulted in a reduced thickness of the mucus layer, increased antimicrobial activity, lower bacterial translocation, and reduction in liver injury (Hartmann et al., 2013). Ethanol exposure also altered the homeostasis of the intestinal immune system by increasing the levels of IFNγ, IL-17, and IgA in a mouse model (López, 2017) and by increasing TNFα levels (Chen, Starkel, Turner, Ho, & Schnabl, 2015) in the duodenal biopsies of patients with AUD.

## Effect of alcohol on the gut microbiota

The interest of studying the gut microbiota in alcoholism is driven by five main observations. First, it has been demonstrated in many experimental models that TLR4 is a key receptor in the development of alcoholic liver disease (ALD) (Uesugi, Froh, Arteel, Bradford, & Thurman, 2001; Uesugi et al., 2002). The activation of TLR4 and its signaling pathways requires the binding of LPS coming from the cell wall of Gram-negative bacteria residing in the gut. This also requires a breach in the gut barrier to allow the translocation of LPS into the portal vein. Other gut-derived bacterial toxins, such as lipoteichoic acid, flagellin, and bacterial hypomethylated (CpG) DNA, have also been implicated in the development of ALD, as mentioned in another review describing the gut-liver axis in AUD (Szabo & Petrasek, 2017). Second, the gut barrier, which is altered in AUD patients, is regulated by specific bacteria, including *Lactobacillus* (Chen et al., 2016), *Bifidobacterium* (Ewaschuk et al., 2008; Khailova et al., 2009; Mennigen et al., 2009), or *Akkermansia* (Everard et al., 2013; Grander et al., 2018).

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These probiotics (*Lactobacillus*, *Bifidobacterium*) or candidate probiotic (*Akkermansia*) have indeed been shown to enhance intestinal integrity by multiple mechanisms, such as maintaining tight junction protein expression, improving intestinal villus/crypt histology, changing mucus thickness, normalizing intestinal cytokines levels, and balancing intestinal immunity. Third, nutrition has a profound influence on gut microbiota composition (Ley, Turnbaugh, Klein, & Gordon, 2006; Sonnenburg et al., 2010), and a large proportion of patients with alcohol dependence are malnourished (Stickel, Hoehn, Schuppan, & Seitz, 2003). Ethanol is not simply a psychotropic substance, but it is also a source of calories (7 kcal/g), which represents more than 40% of the total caloric intake in alcoholic patients (de Timary et al., 2012). Furthermore, dietary interventions using probiotics or prebiotics that modulate the gut microbiota in animal models as well as in AUD patients have been shown to improve gut permeability, inflammation, or liver enzymes. Fourth, the absence of the gut microbiota (in germ-free mice) has been associated with a modulation of the intestinal and hepatic expression of ethanol-metabolizing enzymes, such as alcohol dehydrogenase (ADH), catalase, and cytochrome P450 (Chen, Miyamoto, et al., 2015). Finally, beyond the importance of the gut microbiome-liver axis in alcoholism (Hartmann, Seebauer, & Schnabl, 2015), a growing body of evidence has revealed that the gut microbiota is also an important modulator of brain functions, mood, and behavior (Cryan & Dinan, 2012). In addition to the gastrointestinal symptoms and liver damage, alcohol-dependent patients also suffer from severe psychological symptoms, including depression and anxiety, as well as altered cognitive functions. Altogether, these findings establish a rationale for studying the gut microbiota and its complex interactions with distant peripheral (liver) and central (brain) organs in alcohol dependence.

Several studies have investigated the microbial composition by culture techniques or by analysis of the 16S rRNA gene and found changes in many bacterial taxa, as already reviewed elsewhere (Leclercq, de Timary, Delzenne, & Starkel, 2017). Interestingly, two independent studies (Leclercq et al., 2014; Mutlu et al., 2012) have found that dysbiosis occurred only in some alcohol-dependent patients, and correlated neither with the degree of liver disease nor with the length of abstinence (Mutlu et al., 2012), but was strongly correlated with intestinal permeability (Leclercq et al., 2014). Indeed, it was shown that only alcohol-dependent patients with a leaky gut had alteration of the gut microbiota composition and activity. *Bifidobacterium* and *Faecalibacterium prausnitzii* (a bacterium known for its anti-inflammatory properties; Sokol et al., 2008) were strongly and negatively correlated with intestinal permeability, supporting the idea that certain bacteria actually reinforce the gut barrier. Furthermore, metabolomics analysis revealed that patients with a leaky gut had a high intestinal level of phenol and a low level of indole compounds. These metabolites produced by the bacteria from protein fermentation have been shown, *in vitro*, to have a detrimental and beneficial effect on the gut barrier function, respectively (Bansal, Alaniz, Wood, & Jayaraman, 2010; McCall et al., 2009). One study (Leclercq et al., 2014) strongly suggests an important dialog between the microbes, the microbial metabolites, and the gut barrier function. The same authors also reported that patients with a leaky gut and alterations of the gut microbiota had a more severe form of alcohol dependence, characterized by higher scores of depression, anxiety, and alcohol craving, which are important psychological symptoms predicting the risk of relapse, suggesting gut-brain interactions in this population.

While most of the clinical studies investigating the role of gut microbiota in disease conditions are mostly descriptive (i.e., the abundances of specific bacterial taxa are shown to be higher or lower in the disease group compared to healthy controls), very few studies have investigated the causal link between intestinal microbes and the disease phenotype. Fecal material transplantation, from a human donor to recipient mice, is a new experimental tool to actually prove a cause-effect relationship. This technique has already been used in several pathological conditions such as obesity (Ridaura et al., 2013), intestinal bowel disease (De Palma et al., 2017), and depression (Kelly et al., 2016; Zheng et al., 2016). With regard to alcoholism, a hallmark study conducted by Llopis et al. (Llopis et al., 2016) has shown that a dysbiotic microbiota contributes to the individual susceptibility to alcohol-induced liver damage. Indeed, germ-free mice transplanted with fecal microbiota from patients with severe alcoholic hepatitis exhibited increased intestinal permeability (with change in MUC2 and Reg3$\gamma$ expression), increased bacterial translocation, and increased intestinal and liver inflammation, compared to germ-free mice transplanted with the microbiota of AUD patients without liver lesions, despite similar amounts of alcohol intake. Differences in the composition of the gut microbiota between these two groups of recipient mice were observed, including a higher abundance of the genera *Faecalibacterium* and *Akkermansia* in recipient mice with no liver damage. The profile of bile acids was also different with, for instance, a higher abundance in mice with no liver damage of ursodeoxycholic acid, a secondary bile acid produced by intestinal bacteria that display hepatoprotective properties. The changes in bile acids were associated with changes in the intestinal and hepatic expression of ADH, which in addition to ethanol metabolism is also involved in bile acids metabolism (Langhi, Pedraz-Cuesta, Haro, Marrero, & Rodriguez, 2013). Interestingly, the authors showed that alcohol-induced liver lesions in mice transferred with the microbiota of an alcoholic hepatitis donor could partly be reversed by a subsequent transplant of a fecal sample from a patient without alcoholic hepatitis. While these data prove the causal role of gut microbiota in individual susceptibility to alcoholic liver disease, questions remain whether the disease phenotype is driven by specific bacteria or by specific bacterial metabolites, or most probably by a conjunction of both.

## Effects of the gut microbiota on the brain and behavior in AUD

Although the importance of the changes in the gut microbiota in AUD has largely been demonstrated, direct evidence for a role of the gut microbiota in the brain and behavioral aspects of AUD are currently scarce. Several pathways, however, might explain such an influence. First, alterations of the gut barrier function, leakage of bacterial products through the leaky gut, and development of an inflammation at the gut but also at the liver level may all contribute to the development of a peripheral inflammation that may also trigger the development of a brain inflammation (de Timary, Starkel, Delzenne, & Leclercq, 2017). A peripheral inflammation as manifested by increased circulating pro-inflammatory cytokines or activated peripheral immune cells will indeed pass the blood-brain barrier and induce an inflammation at the level of the microglia or the astrocytes (de Timary, Starkel, Delzenne, & Leclercq, 2017). To correctly elucidate the nature of this cytokine or cell-mediated gut-liver-brain axis, it would in particular be important to better understand the nature of the inflammatory reactions that occur at both the gut and liver levels and that are likely different, the liver possibly constituting a relay for an inflammation arising from the gut bacterial products. We might more precisely imagine that the brain would react differently to specific inflammatory reactions occurring either at the gut or the liver level, and that would 'send' their signals to the brain through the blood circulation. The influence of the peripheral inflammation on the brain may also pass

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through the vagus nerve (Leclercq et al., 2017). Finally, it has also recently been shown that some bacterial products at the gut level, arising from the metabolism of gut substrates by specific bacteria, might also strongly modulate the brain inflammation, as recently demonstrated for tryptophan metabolites (Rothhammer et al., 2016). Hence, the existence of a gut-brain or even a gut-liver-brain inflammatory axis is clear. This is also confirmed by animal and human postmortem studies, which have both confirmed the existence of a brain inflammation in AUD (Robinson et al., 2014). Furthermore, several animal studies have shown that inducing a brain inflammation may influence behavior, and in particular induce alcohol-seeking behavior (Blednov et al., 2011; Robinson et al., 2014). Inflammation therefore appears at the most important pathway for explaining how the gut microbiota influences brain activity, but several other pathways may also be proposed for this gut-brain axis. The gut microbiota exerts, for instance, a strong influence on the secretion of several gut-derived peptides, such as ghrelin, GLP1, or PYY (Delzenne, Neyrinck, Backhed, & Cani, 2011), that may also be related to alcohol behavior (Leggio et al., 2012, 2014), possibly through the regulation of energy balance of appetite, as these dimensions have recently been shown to be affected in AUD (de Timary et al., 2012) and exert an influence on alcohol-seeking behavior. Finally, the gut microbiota also produces, through the metabolism of intestinal products, a great number of substances that may have a direct influence on brain functioning and hence on behavior, independently of the effect on inflammation.

In summary, there exist a great number of pathways by which the gut microbiota may exert an effect on the brain, some of them involving a relay by the liver. Questions remain, however, regarding the type of behaviors they might induce and that participate in the behavioral manifestations of AUD. Currently, changes in gut permeability and gut microbiota have been related to depression, anxiety, and craving (Leclercq et al., 2014), which are cardinal manifestations of AUD, participating in the negative reinforcement of the drinking behavior. Furthermore, abnormal gut microbiota is related to depression that is considered to trigger a tendency to drink in this AUD population (Petit et al., 2017) and may hence increase the severity of the disorder. However, other behavioral aspects are also profoundly affected in AUD, such as, for instance, social interactions. The possibility that the gut microbiota might influence social contacts is supported by observations of a relation between the gut and social behavior, for instance, in autism-spectrum-disorder, both in animals (Hsiao et al., 2013) and in humans (Adams, Johansen, Powell, Quig, & Rubin, 2011; De Angelis et al., 2013). This would clearly deserve to be tested in AUD, where social interactions are largely affected (Maurage, de Timary, Tecco, Lechantre, & Samson, 2015; Maurage et al., 2016; Uekermann, Channon, Winkel, Schlebusch, & Daum, 2007).

## Probiotics and prebiotics to modulate the gut microbiota

Probiotics are live microorganisms which, when ingested in adequate amounts, confer a health benefit on the host (Food and Agriculture Organization of the United Nations, & World Health Organization, 2006). A decrease in *Bifidobacterium* and *Lactobacillus* has been shown in animals exposed to alcohol as well as in patients with alcohol dependence. Consequently, restoration of the beneficial bacteria via oral supplementation could improve alcohol-related disorders. Indeed, in ethanol-fed rats, *Lactobacillus* GG supplementation reduced endotoxemia and alcohol-induced liver injury (Nanji, Khettry, & Sadrzadeh, 1994). Other experimental studies using probiotics in rodents exposed to ethanol have been described in another review (Zhou & Zhong, 2017). In humans, a 5-day supplementation with probiotics *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 during alcohol detoxification had a greater effect on the reduction of liver enzymes than abstinence alone (Kirpich et al., 2008), and a 4-week administration of *Lactobacillus casei* Shirota to alcoholic cirrhosis patients improved the neutrophil phagocytic capacity (Stadlbauer et al., 2008). Additionally, in patients with alcoholic cirrhosis, administration of VSL#3 (a mixture of 8 different strains of bacteria) significantly reduced the levels of plasma cytokines TNFα, IL-6, and IL-10 (Loguercio et al., 2005). These data suggest a beneficial effect of probiotics on the gut-liver axis in alcohol-dependent patients. But what about the gut-brain axis? Several clinical trials have demonstrated the beneficial effects of probiotics on psychological symptoms (Akkasheh et al., 2016; Messaoudi et al., 2011; Steenbergen, Sellaro, van Hemert, Bosch, & Colzato, 2015) and brain activity (Tillisch et al., 2013). To our knowledge, no study has assessed the potential benefit of probiotics on brain alterations and psychological symptoms in patients with alcohol dependence.

Whereas probiotics use live microorganisms, prebiotics are non-viable substrates (dietary fibers) that serve as nutrients for beneficial microorganisms harbored by the host. They are therefore expected to stimulate the growth of a broad range of members of the gut microbial community (Bindels, Delzenne, Cani, & Walter, 2015), including *Faecalibacterium prausnitzii*. The most recent definition of a prebiotic indicates that it is a substrate selectively utilized by host microorganisms conferring a health benefit (Gibson et al., 2017). Dietary prebiotics that have most extensively been documented to confer health benefits in humans are the non-digestible oligosaccharides fructans and galactans. Those are preferentially metabolized by bifidobacteria and are mostly found in fruits and vegetables (Roberfroid & Delzenne, 1998). Prebiotics exert their health effects through the production of beneficial metabolites such as short-chain fatty acids (acetate, propionate, and butyrate) with antimicrobial activity, through lowering of the intestinal pH to inhibit pathogen growth, or through reinforcing the colonic defense barrier and exhibiting anti-inflammatory properties (Hamer et al., 2008). Studies exploring the effect of prebiotics on alcohol-related disorders are somewhat limited. In rats, oat supplementation reduced gut leakiness and ameliorated alcohol-induced liver damage (Keshavarzian et al., 2001; Tang, Forsyth, Banan, Fields, & Keshavarzian, 2009). In mice, treatment with fructo-oligosaccharide partially restored the level of Reg3γ, reduced bacterial overgrowth, and lessened alcoholic steatohepatitis (Yan et al., 2011). Regarding the gut-brain axis, consumption of prebiotics in rats has been associated with neurochemical changes, including increased hippocampal expression of brain-derived neurotrophic factor and glutamate receptor (Savignac et al., 2013), which are involved in the regulation of numerous behaviors such as anxiety, depression, cognitive performance deficits, and addiction (Li & Wolf, 2015).

## Conclusion

Recent research suggests that the gut microbiota may affect brain functions and behaviors. Alcohol dependence, together with other substance-use disorders as well as eating disorders, is associated with altered neurobiological pathways in specific brain areas involved in reward processing (Temko et al., 2017). While preclinical work carried out in germ-free mice has demonstrated the bacterial influence on specific genes in the striatum (Diaz Heijtz et al., 2011), the amygdala (Stilling et al., 2015), the hippocampus (Neufeld, Kang, Bienenstock, & Foster, 2011), and prefrontal cortex (Hoban et al., 2016), little is known about the influence of intestinal bacteria on the neurobiological processes in humans with substance-use disorders, as highlighted by a recent systematic review (Stadlbauer et al., 2008).

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Accumulating data show that severe dysbiosis occurs in some but not all AUD patients (Leclercq et al., 2014; Llopis et al., 2016; Mutlu et al., 2012), and is not linked to the history of alcohol abuse or the amount of alcohol consumed. One may hypothesize that initial microbial differences are present before the development of alcohol dependence and that the combination of host genetics, commensal microbes, and bioactive metabolites together with alcohol exposure may condition the disease severity and susceptibility to develop liver disease.

The capacity to transfer certain host metabolic features related to alcoholism via gut microbiota transplantation highlights the power of the humanized models, which is particularly relevant in alcoholism where non-transplanted animal models poorly mimic the whole spectrum of the disease, especially in terms of liver inflammation and psychological dependence. Furthermore, modulation of the gut microbiota by the use of probiotics or prebiotics represents a promising and safe therapeutic approach in the management of alcohol dependence. Prospective, randomized, placebo-controlled clinical trials are definitely needed to evaluate the effects of probiotics and/or prebiotics on alcohol dependence, and more particularly on different behavioral aspects of addiction, such as depression, anxiety, stress response, impaired cognition, impulsivity, and drug-seeking behavior.

## Conflict of interest

The authors declare no conflict of interest.

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