



# Gut Microbiota Role in Liver Regeneration: Evidences and Novel Insights



**Davide Frumento\***

*Department of Health Sciences, University of Genoa, Italy*

**\*Corresponding author:** Davide Frumento, Infectious Diseases Unit, Hospital San Martino Largo Rosanna Benzi 10 16132 Genova (GE), Italy

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## Abstract

Human pathophysiological status highly depends on microbiota activity; its presence is in fact necessary to a healthy development, as well as for backing up immune system in the defense from pathogens. Gut microbiota also acts as a metabolic player that takes part in host metabolism by partially regulating bile acids (BAs) metabolism, as well as farnesoid X receptor (FXR) signalling. In fact, if microbiota functions are totally or even partially impaired, its role in supporting both BAs and FXR pathways will be undermined too, resulting in a diminished liver regeneration function. Hepatic pathologies have been associated to impaired gut microbial diversity, that can trigger a positive feedback cycle that worsen liver injury and obstruct liver regeneration process. Alcoholic liver disease subjects were typically infected by Bacteroides species and expanded Proteobacteria ones. Thus, it can be inferred that an intimate relationship between microbiota, hepatic metabolism and injury as well as regeneration is standing. Within this complex scenario, it is not surprising that the gut-liver axis could be also part of the regenerative mechanisms that, under certain circumstances, occur within the hepatic environment. This opinion paper aims to put together some of the evidences related to this thesis in order to consolidate it and give new insights about it.

## Introduction

A large majority of human organism areas happens to be massively colonized by a diversified microbial community and the association of these bacterial pools makes up the so-called microbiota. This enormous population is mostly constituted by bacteria and fungi. These microorganisms are estimated to outnumber human cells Bianconi et al. [1], Hao & Lee [2] and Whitman et al. [3]. Human pathophysiological status highly depends on microbiota activity; its presence is in fact necessary for healthy development, as well as for backing up immune system in the defense from pathogens Grice et al. [4] and Keijser et al. [5]. Microbiota is held responsible for a large number of key physiological functions in human body; in fact, it was recently reported that it plays a pivotal role in tastes perceptions Frumento [6] by secreting acids that, degrading esters molecules in mouth, mouth bacteria exert an important influence on both oral and retropharyngeal sensing. Moreover, microbiota has been demonstrated to be involved in HCV (Hepatitis C virus) infection, favoring it both when bacterial composition balance is lost and phylotypes diversity is lowered Frumento [7]). Within this complex scenario, it is not surprising that the gut-liver axis could be

also, part of the regenerative mechanisms that, under certain circumstances, occur within the hepatic environment. This opinion paper aims to put together some of the evidences related to this thesis in order to consolidate it and give new insights about it.

## Liver Regeneration: Bile Acids and Gut Microbiota Interplay

Gut microbiota acts as a metabolic player that actually takes part in host metabolism Semenkovich et al. [8], by partially regulating bile acids (BAs) metabolism, as well as farnesoid X receptor (FXR) signalling Sayin et al. [9] and Parséus et al. [10]. Although surplus BAs can contribute to impair liver regeneration and cause liver injury, they have also been proven to be critically associated to proper restoration of both liver mass and functionality. Plasmatic BAs levels were shown to be positively related with liver regeneration in rabbits, tailing portal vein embolization Hoekstra et al. [11]. In fact, a starting enlargement in BAs pool size quickened the regenerative process, which brings us to hypothesize that if excess

concentrations can inhibit regeneration, moderate BAs levels enhanced hepatocyte proliferation process Huang et al. [12]. Partial hepatectomy-induced (PH) liver regeneration was found to remarkably delayed in rats when BAs pool dimension was lowered by cholestyramine (namely, a BAs sequestrant molecule) Dong et al. [13]. Both genetic and surgical impairment of physiological BAs enterohepatic circuit badly lowered liver regeneration after PH in mice. PH plus ileal resection caused a decreased liver regeneration capability, probably due to loss of BAs reuptake in the ileum tract

Naugler [14] and Medeiros et al. [15]. Such findings evidence BAs circuit through the gut-liver axis as a pivotal regulatory actor within the liver regeneration process. Both the proliferative and harmful effects of BAs on hepatocytes highlight the importance of a proper BAs homeostasis maintenance in order to ease liver repair.

Moreover, FXR total KO mice showed a retarded liver regeneration process likely due to a BAs synthesis dysregulation Huang et al. [12]. Gut FXR was also proven to promote liver regeneration via upregulation of murine FGF15, an ileal-secreted enterokine induced by FXR in order to inhibit BAs overproduction Uriarte et al. [16] and Schaap et al. [17]. Furthermore, gut FXR KO hampered liver regeneration as an outcome of insufficient FGF15 activity, which was recovered exogenous FGF15 administration Zhang et al. [18]. Interestingly, FGF15 KO mice showed significantly increased mortality after liver resection, probably due to hepatic failure if compared to control ones Uriarte et al. [16] and Kong et al. [19]. It has also to be said that hepatocyte-specific FXR KO mice also displayed delayed liver regeneration due to deactivation of both HGF and Cyclin D-mediated signalling Borude et al. [20]. Taken together, these findings clearly indicate that if microbiota functionality is totally or even partially impaired, its role in supporting both BAs and FXR pathways will be undermined too, resulting in a diminished liver regeneration function.

### Liver Diseases: The Role of an Altered Microbiota

Hepatic pathologies have been associated to impaired gut microbial diversity, that can trigger a positive feedback cycle that worsen liver injury and obstruct liver regeneration process. Alcoholic liver disease subjects were typically infected by Bacteroides species and expanded Proteobacteria ones. Such an intestinal dysbiosis was also positively linked to high serum endotoxin levels, probably due to excessive bacterial translocation Mutlu et al. [21]. Endotoxemia, along with lowering in Bacteroides presence is expected to partially disrupt liver regeneration. The investigation of both alcoholic and non-alcoholic liver steatosis has been proven to be precious to observe the outcomes of intestinal microbiota alterations. Non-alcoholic steatohepatitis causes an innate immune activity, which stirs hepatic inflammation via cytokines (e.g. TNF $\alpha$ ) Tsujimoto et al. [22].

Obesity-induced non-alcoholic steatohepatitis was shown to trouble intestinal microbiota composition by lowering total microbial diversity, probably by Bacteroidetes species shrinkage De Wit et al. [23]. Liver lipid levels in individuals suffering from choline deficiency have also been shown to unbalance gut microbial diversity Spencer et al. [24]. An experimental therapy employing an association of five Chinese herbs (Compositae, Polygonaceae, Zingiberaceae, Clusiaceae, Rubiaceae) was demonstrated to enhance proliferation of short chain fatty acid producer *Collinsella*, as well as improving steatosis in rats Yin et al. [25]. Gut microbiota alteration associated with steatosis lowered Bacteroidetes abundance; this particular condition may lead to gut dysbiosis and propagation of hepatic injury. Other pathologies, such as gastrointestinal diseases,

can influence hepatic damage too, acting on gut microbiota. In fact, in a rat model of irritable bowel syndrome, *Lactobacillus casei* and *Bifidobacterium lactis* diet integration relieved inflammation and apoptosis in both the liver and the colon tract Bellavia et al. [26]. Thus, it can be inferred that an intimate relationship between microbiota, hepatic metabolism and injury as well as regeneration is standing.

### Conclusion and Novel Insights

After a careful consideration of the above analyzed studies, it can be said that microbiota homeostasis plays a pivotal role in maintaining the physiological status of liver regeneration capability. In fact, a microbial diversity unbalance can result in a metabolic alteration of BAs metabolism, as well as in the FXR signalling impairment; given that such a set of metabolic perturbations was demonstrated to result in lowering the hepatic regeneration functionality, it is safe to conclude that a healthy status of microbiota is an undirect factor needed to have a normal liver regeneration functionality. Plus, it was extensively assessed that gut microbial diversity alterations are linked to liver pathologies and trigger a positive feedback cycle that worsen liver injury and obstruct liver regeneration process.

Gut-liver axis is therefore a biological pathway that is helping the scientific community to strengthen the idea that microbiota is a semi-environmental factor that decisively influences both human physiological and pathological statuses in different organic districts. These findings suggest that, since a every ethnic group corresponds to a different microbial composition within microbiota, a healthy bacterial configuration can thus vary between different ethnicities, most likely due to a diverse set of metabolic adapting reactions to the particular geographic areas during human evolution. Moreover, a new research scenario is opening and leading investigators to study the genetic and environmental influences on such an adaptation, deepening our knowledge about whether microbial diversity is linked to genetics or not and, if yes, what is the extent of such a correlation.

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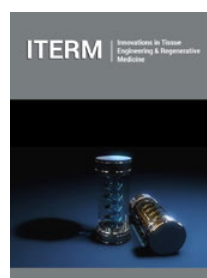
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