

Microbiota and HCV Infection Interplay



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Abstract

Hepatitis C virus (HCV) is held responsible for about 17.5% of acute hepatitis cases and after acute infection, roughly 65% of patients develops a chronic infection. Intestinal microbiota's relevance in the pathogenesis of HCV-induced chronic liver diseases is a promising topic within scientific community. Anyway, its role in chronic HCV infection is still not completely unraveled and it needs more detailed investigations. Although results on relationships standing between human microbiota and HCV infections are lacking, the few published articles are highly inspirational for both further studies and theoretical researches, giving a starting substrate to hypothesize the mechanisms underlying the relationships between microbiota and HCV in the context of gut-liver axis. The aim of this short review is to summarize the state of the art of microbiota/HCV interactions and possibly give a novel point of view based on the articles' conclusions, using an eagle-eye perspective that will allow to open a door to new research studies concerning HCV infections.

Introduction

Several human body districts are colonized by a microbial community and the gathering of these pools makes up the microbiota. This huge population is formed by bacteria, fungi and these microorganisms are estimated to outnumber human cells [1-3]. Human physiological status greatly depends on microbiota, in fact its presence is necessary for a normal development, as well as for supporting immune system in the protection of the host from pathogens [4,5]. Intestinal microbiota's relevance in pathogenesis of HCV-induced chronic liver diseases is a rising topic among scientific community. Anyway, its role in chronic hepatitis C virus (HCV) infection is still unclear and it needs more focused studies [6]. Microbiota nutritionally competes with pathogens for resources and colonization sites and it gives fundamental signals for immune priming, sustaining immune system correct development [7-10]. It has a controversial role, since it can limit or promote viral infection, or have no effect, but direct or indirect effects on viral infection itself can take place. For example, microbiota (or its metabolites) may interact with viral particles, altering response or infectivity [11-14]. Intestinal microbiota has also been recognized to have a pivotal importance in autoimmune diseases such as type 1 diabetes (T1D) [15-17]. The aim of this short review is to reassess the state of the art of microbiota/HCV interactions and possibly give a novel point of view based on the reviewed studies, using an eagle-eye perspective.

The HCV infection

Hepatitis C virus (HCV) is held responsible for about 17.5% of acute hepatitis cases and it was reported that, after acute

infection, roughly 65% of patients develops a chronic infection [18]. According to the WHO (World Health Organization) statistics, HCV is currently infecting about 170 million people worldwide. Patients suffering from Chronic Hepatitis C (CHC) have a high probability to develop serious complications, i.e. cirrhosis and hepatocellular carcinoma (HCC) [19-21]. Under an epidemiological point of view, it was reported that HCV is associated with several extrahepatic manifestations such as type 2 diabetes mellitus, insulin resistance, oral manifestations and glomerulopathies [22-25].

Microbiota and viral infections

Since microbiota typically colonizes sites used by viruses to introduce themselves into hosts, its presence can in some cases affect the infection outcome. It was in fact reported that the commensal microbiota of *Aedes aegypti* (an insect vector) indirectly mitigates Dengue viral transmission [26]. Mosquitoes in which the commensal population is killed by antibiotic molecules show higher viral titers with the respect to those in which antibiotics are not administered. Moreover, mosquitoes having their natural microbial population highly express a broad set of immune-related genes, such as those encoding antimicrobial peptides modulated by Toll-like receptor (TLR) pathway (Xi et al. 2008).

On the other hand, while it is true that microbiota can be pivotal to fight viral infections and therefore shift the infective process balance, it may also enhance viral infection, either in a direct or indirect way. Previous studies demonstrated the indirect promoting activity exerted by microbiota on virus

replication, i.e. the viral infection enhancing via the proliferative stimulation or target cells activation [27]. Moreover, this concept is especially applicable for retroviruses targeting proliferating cells, in fact, murine leukemia virus (MuLV)-infected germ-free mice are show a mild resistance to virally induced leukemia if compared to conventional murine models [28,29]. Conversely, sheep red blood cells-immunized MuLV-infected mice show a significant increase in leukemia development, comparable to that of infected specific pathogen free (SPF) mice [29]. Previous investigations show that viruses belonging to three distinct families partially depend on commensal microorganisms in order to perform an efficient replication/transmission process [30,31]. Kuss et al. [30] demonstrated that poliovirus-susceptible mice administered with antibiotics exhibit lower mortality rates after poliovirus infection if compared to untreated ones. Relevantly, virus replication in murine guts is highly relying on microbiota, in fact antibiotic-treated and germ-free mice secrete poorly virulent viruses. Both Gram-positive and Gram-negative bacteria incubated with poliovirus highly promote its infectivity in cultured cells. Such a phenomenon does not need live bacteria, because surface polysaccharides, like peptidoglycan (PG) and lipopolysaccharides (LPS), are sufficient to exert such an effect on viral infectivity. Significantly, these results were not solely related to poliovirus, since the reovirus infection was found to be more severe if gut microbial population were present.

HCV and microbiota

To date, Pubmed Archive (www.ncbi.nlm.nih.gov/pubmed/) reports few researches on relations standing between HCV and microbiota have been published. Yet, this interplay was not fully understood. One of the most recent published studies reported that intestinal microbiota of 95 patients chronically infected with HCV, with and without cirrhosis, greatly differs between cirrhotic and non-cirrhotic patients. Moreover, this study highlighted that the stage of both HCV infection and liver disease is linked with a lowered alpha diversity, and it was inferred that this could be due to a direct cross-talk between HCV and host's bacterial populations or indirect relations enhanced by immune system [32]. So, this is an example in which microbiota could be held responsible of easing both viral activity once patient is infected and stage of cirrhosis. So, phylotypes number appear to be inversely proportional to the occurred complications.

Interestingly, it was demonstrated that mucosal gut microbiota composition is altered in patients with Chronic Hepatitis C (CHC) with respect to cirrhotic ones and those suffering from hepatocellular carcinoma (HCC). An increase of Proteobacteria and a reduction of Bacteroidetes and Firmicutes phyla was reported in CHC, HCC and cirrhotic individuals, suggesting the existence a pathogenic role of gut microbiota in the HCV-related liver disease and HCC development [33]. So, in this case, a precise unbalance in bacterial populations is correlated with the virus and is long-term complications. Thus, it can be said that preservation of gut microbiota composition, employing various strategies like prebiotics and probiotics

seems to be a hopeful instrument for preventing or treating the progress of liver disorders associated with HCV [34-36]. Interestingly, stool samples analyses from six HCV patients and eight healthy individuals gene sequencing showed that the alpha-diversity of the healthy individuals gut microbiomes was higher than the patients one. Common points with the above cited work can be found, in fact, although Bacteroidetes were more abundant in HCV subjects, healthy ones had more Firmicutes, Proteobacteria, and Actinobacteria. Moreover, Bifidobacterium (probiotic genus), was only detected in healthy individuals [37]. Plus, a cohort of 105 HCV cirrhotics was examined in order to understand if viral eradication could impact on microbiota composition. No significant differences in overall microbiota diversity (UNIFRAC $P=0.3$) between groups with/without SVR (Sustained Virological Response). So, curing the infection does not bring any variation in gut microbiome [38]. However, results about microbiota analysis of a large population of HCV individuals are lacking.

Conclusion

It can be concluded that, although researches on relationships standing between human microbiota and HCV infections are lacking, the few published papers are highly inspirational for both further studies and theoretical investigations. As stated above, HCV infection and related liver disorders are influenced by microbiota, namely by loss of bacterial composition balance and lowering of phylotypes diversity. Taken together, these findings allow to point out that the gut-liver axis is very important within the HCV infection context and is particularly influential on its liver complication. It could be therefore useful to perform fecal transplantations on patients that are found in a condition of gut dysbiosis, in order to restore the phyla pattern. It remains unclear if particular microbiota alterations could act as a predisposing factor for an especially aggressive HCV infection or if such an infection causes dysbiosis.

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