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Review

Is it time for microbiome-based therapies in viral infections?

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ABSTRACT

Infectious diseases related to viruses, as well as bacterial pathogens, abound in all parts of the world, burdening health and economy. Thus, there is a dire need to find new prevention and treatment strategies to improve clinical practices related to viral infections. Human gut contains trillions of bacteria which have regulatory roles in immune development, homeostasis, and body metabolism. Today, it is difficult to find any prominent viral infection that hasn't had any link with the human gut microbiota. In this opinion-based review article, I argued the significance of manipulating human gut microbiota as novel therapeutics through probiotics or FMT in alleviating complexities related to viral infections, and pinpointed bottlenecks involved in this research.

1. Introduction

In today's world, infectious diseases are evolving rapidly with tremendous effects on the health and well-being of people throughout the world. Emerging/re-emerging viral infections, such as Ebola and Zika virus diseases, and severe acute respiratory syndrome-related coronaviruses (SARS and MERS) present a great threat to public health due to their rapid transmission and associated severe health conditions that may lead to death. Recently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as COVID-19) emerged in Wuhan, China, and infected tens of thousands of people and at least 1,153,000 people have died since the first patient appeared on December 12, 2019, and this novel virus is currently affecting 215 countries/territories around the globe. Amid these burgeoning crisis related to viral infections, scientific community should spotlight elegant scientific outcomes to combat viral infections and generate knowledge on potential scientific methods that may reduce the burden of these viral infections through better clinical practices. Human body contains trillions of microbes residing within and upon our body - termed commensal microbiota, which have a significant role in eliciting immune response, and maintaining homeostasis and host health. Gut microbiome profiling has a great role in clinical risk prediction and even the extrapolation of the genetic signatures of gut microbes can possibly predict probability of death over the next 10–15 years (Salosensaari et al., 2020). From 2013 to 2017, 12,900 articles related to gut microbiota were published, which account for 4/5 of the total number of publications in the last 40 years – signifying the importance of gut microbiota and advancement in this research (Cani, 2018).

The metagenomics data available on healthy and diseased subjects indicate that human commensal microbiota is an important marker of health and disease in various disorders including viral infections, where it confers host protection against viral infections. Many viral infections lead to health complications and many of which are associated with dysbiosis of the gut microbiota (Li et al., 2019). Dysbiosis as a result of viral infections often results in the abundance of pathogenic bacteria, and this situation can dramatically affect disease prognosis leading to chronic illness. Efficacy of vaccines often becomes limited due to frequent mutations in viruses (Zost et al., 2017). It is tempting to speculate that modification of the gut microbiota through probiotic interventions may alleviate many health complications of viral infections. Many probiotic bacteria not only affect viral infections, but administration of suitable probiotics in several viral infections, especially involving respiratory and gastrointestinal complications show clinical advantages (Park et al., 2013). In this article, relationship between gut microbiota dysbiosis and viral infections is discussed and the possibility of using microbiome-based therapies in viral infections to alleviate their complications is evaluated.

2. Gut microbiota and viral infections

The human microbiome has gained increasing interest over the last 15 years because of its role in regulating a number of metabolic activities and complex diseases in the human body. Disruption of microbial integrity and diversity is correlated with various pathological conditions. Many viruses come in direct contact with the gut microbiota in mucosal surfaces which has adapted several direct and indirect

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mechanisms to cause their evasion or to provide protection against their infection through fine-tuning of the innate immune response. Following interaction between viral surface proteins and cellular surface proteins, a host response is initiated, which leads to the first wave of cytokines and chemokines production. In many gut bacteria, flagellin (the ligand of TLR5) elicit a robust activation of pro-inflammatory cytokines and chemokines against viruses. Type I and type II interferons (IFN-I and INF-II), both having immunoregulatory functions, are the major groups of signaling proteins involved in combating viral infection and in type II immune responses (Lee and Ashkar, 2018). Intestinal dysbiosis could create aberrant immune responses which can lead to abnormal production of antiviral cytokines (Schirmer et al., 2016). Thus, gut microbiota dysbiosis in viral infections affect immune response of the body which counteracts viral infections. A coevolution of human immune system and gut microbiota is a result of crosstalk between the two systems. Therefore, a variation of vaccine response in different individuals is due to variation in gut microbiota as a result of different age, diet and many other factors (Zimmermann and Curtis, 2018). Bacterial abundance of Actinobacteria (mainly *Bifidobacterium longum* subsp *infantis*), Proteobacteria, and Bacteroidetes has been reported to positively correlate with T-cell responses to different vaccines (Acharya et al., 2020). Mechanisms behind the protective role of probiotics in different viral infections are highlighted in Table 1. The following sections will provide evidence of gut microbiota dysbiosis in common viral infections:

2.1. Gut microbiota dysbiosis in influenza and other respiratory viral infections

Every year the soaring number of influenza A virus (IAV)-associated mortality and morbidity rates, resulting in death of hundreds of thousands of people annually, raise question on our success in combating viral infections - necessitating the development of new therapies with potential to reduce the severity of IAV-related infections. The link between the respiratory tract and intestinal tract can be exemplified by intestinal complications during respiratory diseases and various respiratory complications associated with abdominal diseases (Minodier et al., 2017). Wang and others demonstrated that gut microbiota dysbiosis as a result of influenza infection is mediated by IFN- γ (INF-I and INF-II) produced by lung-derived CCR9 and CD4⁺ T cells which are recruited into small intestine, and mediated by the CCL25-CCR9 cytokine axis. There was a significant increase in Th17 cells in the small intestine after the infection caused by H1N1 influenza virus, causing intestinal immune injury, and it was reduced after neutralizing IL-17A (Wang et al., 2014). Immune-mediated inappetence and weight loss, induced as a result of cellular immune response to influenza viral infection, alters gut microbiota too (Groves et al., 2020).

The dysbiotic microenvironment of intestine as a result of influenza virus leads to robust depletion of many important bacterial groups, disruption of mucosal layers, and production of high quantity of antimicrobial peptides in Paneth cells. A recent study hypothesized that gut microbiota dysbiosis leads to bacterial superinfection in lungs. It was reported that influenza virus alters short chain fatty acids (produced as a result of dietary fiber fermentation) production and cecal and intestinal microbiota. A reduction in acetate production increases vulnerability to lungs to pneumococcal infection (Sencio et al., 2020).

The commensal microbiota has been reported to suppress the influenza viral infection through various mechanisms involving the generation of virus specific CD8⁺ T and CD4⁺ cells, and through their regulatory role in immunity in the respiratory mucosa by activating inflammasomes (Ichinohe et al., 2011). For example, a study showed that chickens with depleted microbiota with antibiotics became more vulnerable to avian influenza virus than the chickens in which microbiota was restored by fecal microbiota treatment (FMT) (Yitbarek et al., 2018). Modulation of the human gut microbiota through probiotics is a strategy to combat influenza virus infection (Table 1).

Many other viruses infecting respiratory systems, for instance corona

viruses, also perturb respiratory and gut microbiota and predispose patients to infections with many bacterial pathogens which may have serious clinical consequences. A novel corona virus, with 82% genome sequence similarity with SARS appeared at the end of 2019 and caused an outbreak of viral pneumonia, where infected people showed respiratory and enteric symptoms. Despite social distancing, hygiene, and availability of methods for the rapid detection of COVID-19, it is inevitably spreading, burdening the health care systems. At the moment, there is no effective antiviral drug against COVID-19 and vaccines do not seem to be available for commercial use in the near future. SARS-CoV-2 shows a spectrum of health complications ranging from mild flu, fever, and cough to pneumonia, and many life-threatening complications such as multiorgan failure, encephalopathies, and acute respiratory distress syndrome (ARDS). SARS-Cov-2 may also lead to neurological symptoms (confusion, ataxia, cerebrovascular disease, dizziness, muscle pain, and seizures) (Acharya et al., 2020). Therefore, it is highly desirable to find some alternate and effective methods to combat this virus.

This virus not only transmits through the respiratory route, but there is substantial evidence of its transmission through the fecal-oral route (Ding and Liang, 2020; Wang et al., 2020). From the early reports of epidemiological and clinical features of patients in Wuhan, about 2–10 % patients showed gastrointestinal illness characterized by diarrhoea, abdominal pain, and vomiting (Chen et al., 2020a). It was first speculated that SARS-CoV-2 may also alter human gut microbiota through the receptors of angiotensin-converting enzyme 2 (ACE2) receptor, a carboxypeptidase (Gao et al., 2020). Now it has been recently confirmed that SARS-CoV-2 uses ACE2 as a cellular entry receptor to enter into cells and the serine protease TMPRSS2 for S protein priming (Hoffmann et al., 2020). ACE2 is abundantly present in humans in type-II alveolar epithelial of the lung and small intestine, which might provide possible routes of entry for the SARS-CoV-2. Evidence has been produced for the abundant expression of ACE2 cells of duodenal, gastric, and rectum epithelia in case of SARS-CoV-2 infection (Xiao et al., 2020). The aforementioned study also reported the presence of viral RNA in fecal sample of patients (39 out of 73 patients). Another study has also provided the evidence of ACE2 and TMPRSS gene expression in colon, small intestine, and stomach epithelia (Meng et al., 2020). In the intestinal epithelial cells, ACE2 acts as a key regulator of the renin-angiotensin system (RAS), and it regulates gut microbial ecology linking it with amino acid homeostasis and intestinal inflammation (Hashimoto et al., 2012). ACE2 is involved in the degradation of Angiotensin II (Ang II), resulting in Angiotensin-(1–7), which reduce oxidative stress and inflammation caused by Ang II. The use of ACE2 by SARS-CoV-2 in intestine, resulting in dysbiosis in gut microbiome links the role of ACE2 in viral infection through the modulation of gut microbiota. ACE-2 activity is reduced, whilst the RAS is activated in case of SARS-CoV-2 infection which leads to inflammation in intestine. The S protein of the virus has also been reported to use sialic acids linked to host cell surface glycoproteins and gangliosides (Fantini et al., 2020).

Some preliminary studies have already indicated gut dysbiosis in SARS-CoV-2 patients in Zhejiang province, China (Xu et al., 2020). The results emphasized the importance of monitoring gastrointestinal functions in SARS-CoV-2 patients and the use of probiotics for balancing intestinal microbiota to reduce secondary infections related to altered pathogenic bacteria. In another study, when gut microbiota of 15 patients at different stages of COVID-19 (mild, moderate, severe, and critical) was taken 2–3 times over a period of one week and compared with the gut microbiota of 15 healthy subjects, significant changes in gut microbiota in relation to disease severity and recovery were noticed – depletion of beneficial microbiota and enrichment of opportunistic pathogens. COVID-19 patients sometimes have the hyper-inflammatory state in which a storm of cytokines emerges and damages mitochondria, which also aggravates the situation by causing microbial dysbiosis (Saleh et al., 2020). An increase in abundance of *Coprobacillus*, *Clostridium hathewayi*, and *Clostridium ramosum*, whereas a decrease in abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory

Table 1
Mechanism behind the role of probiotics in ameliorating the effects of viral infections.

Probiotic/gut microbiota	Mechanism against viral infection	Type of the virus	Type of the model	Reference
<i>Bifidobacterium longum</i> BB536	An increase in the NK cell activity and the bactericidal activity of the neutrophils	Influenza virus	A clinical trial	(Namba et al., 2010)
<i>B. longum</i> BB536	Increase in IFN γ and IL-6	Influenza virus	A mouse model	(Iwabuchi et al., 2011)
Gut microbiota	Upregulation of the TLR7 signaling pathway for the activation of inflammasomes	Influenza virus	A mouse model	(Wu et al., 2013)
<i>Lactobacillus paracasei</i> , <i>Lactobacillus casei</i> , and <i>Lactobacillus fermentum</i>	Increase in IFN- γ in the serum and sIgA in the gut of humans	Influenza virus	A single center, double-blind, randomized, controlled, prospective trial	(Zhang et al., 2018)
<i>Lactococcus lactis</i> JCM 5805	Up-regulation of secreted IgA levels in saliva and phagocytotic activity of neutrophils.	Influenza virus	A randomized, double-blind controlled trial in healthy subjects	(Fujii et al., 2017)
<i>Lactobacillus rhamnosus</i> GG	Improvement of immune gene transcriptional responses during early infection and specifically upregulation of Type-I IFN pathways.	Influenza virus	A mouse model	(Kumova et al., 2019)
<i>Enterococcus faecium</i> NCIMB 10415	Through direct physical interaction and strengthening of innate defense at the cellular level.	Influenza virus	Porcine macrophage cell line	(Wang et al., 2013)
<i>Lactobacillus plantarum</i> DK119	Production of high levels of cytokines IL-12 and IFN- γ in bronchoalveolar lavage fluids and modulation of host innate immunity of dendritic and macrophage cells	Influenza virus	A mouse model	(Park et al., 2013)
<i>Lactobacillus gasseri</i> LG2055	Inhibits virus replication by up-regulating the expression of antiviral genes (for example, Mx1)	Influenza virus	A mouse model	(Nakayama et al., 2014)
<i>L. rhamnosus</i> M21	An increase in the levels of interferon- γ , interleukin-2, and sIgA,	Influenza virus	A mouse model	(Song et al., 2016)
<i>Bifidobacterium bifidum</i>	Modulation of humoral and cellular immune responses and regulation of Th1/Th2 immune responses against influenza infection.	Influenza virus	A mouse model	(Mahooti et al., 2019)
<i>Bifidobacterium animalis</i>	An anti-influenza effect as a result of probiotic metabolites (valine and coenzyme)	Influenza virus	A mouse model	(Zhang et al., 2020)
<i>Bacillus subtilis</i> OKB105	Bacterial surfactin with potential to absorb viral particles	Transmissible gastroenteritis corona virus	Intestinal porcine epithelial cell line	(Wang et al., 2017b)
<i>Lactobacillus</i> species	An increase in the expression of the CD4 receptor that is used to block HIV transmission.	HIV infection	Study of the cell surface protein of <i>Lactobacillus</i>	(Su et al., 2013)
<i>L. rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14.	An increase in CD4 ⁺ T cells which decrease upon HIV infection	HIV infection	Human trials on HIV-infected patients	(Anukam et al., 2008)
Mixed probiotics	Epithelial healing, and restoration of the intestinal CD4 ⁺ T-cell population	HIV infection	Human trials on HIV-infected patients	(Kazemi et al., 2018)
Probiotic Visbiome®	Reduce systemic immune activation and accelerate gut immune restoration	HIV infection	A prospective, double-blinded, randomized, placebo-controlled, multicenter pilot study on HIV-infected patients	(Kim et al., 2016)
<i>Lactobacillus acidophilus</i> ATCC 4356	CD4 (human HIV receptor) carrying probiotic strain showed the ability to adsorb HIV particles	HIV infection	<i>In vitro</i> trial	(Wei et al., 2019)
<i>Clostridium butyricum</i> in combination with <i>Bifidobacterium infantis</i>	An improvement in patient's cognition, improved gut microbiota homeostasis, an obvious reduction in venous ammonia, and an improved intestinal mucosal barrier	Hepatitis B virus (HBV)-induced liver cirrhosis.	Human trials on HIV-infected patients	(Xia et al., 2018)
<i>Bifidobacterium adolescentis</i> SPM0212	The Mx GTPase pathway-dependent inhibition of hepatitis B virus	HBV	Use of cell culture medium and virus particles	(Lee et al., 2013)
<i>Enterococcus faecalis</i> strain FK-23	A significant decrease in serum alanine aminotransferase level	Hepatitis C infection	A clinical trial	(Oo et al., 2016)
<i>Lactobacillus gasseri</i> SBT2055	Causing a decrease in the expression of pro-inflammatory cytokines in the lung	Respiratory syncytial virus	A mouse model	(Eguchi et al., 2019)
<i>Bifidobacterium lactis</i> Bb12	Augmented fecal sIgA concentration, and an increase in anti-poliovirus-specific IgA and anti-rotavirus-specific IgA	Polio and rotavirus infection	A prospective, randomized, double-blind, controlled clinical trial on formula-fed infants	(Holscher et al., 2012)
<i>Streptococcus thermophilus</i> DSM 32345, <i>L. paracasei</i> DSM 32243, <i>L. acidophilus</i> DSM 32241, <i>L. plantarum</i> DSM 32244, <i>Lactobacillus helveticus</i> DSM 32242, <i>B. lactis</i> DSM 32247, <i>Lactobacillus brevis</i> DSM 27961, and <i>B. lactis</i> DSM 32246	Not known (possibly reduction of oxidative stress through Nrf2 and HO-1)	COVID-19	Human subjects	(d'Ettoire et al., 2020)
<i>Bacteroides fragilis</i>	Capsular polysaccharide A of <i>Bc. fragilis</i> induces IL-10 producing CD4 ⁺ and CD8 ⁺ T cells which prevent the viral infection	Herpes simplex encephalitis (HSE)	A mouse model	(Ramakrishna et al., 2019)

bacterium) was reported in disease severity. *Bacteroides dorei*, *Bacteroides massiliensis*, *Bacteroides thetaiotaomicron*, and *Bacteroides ovatus*, which downregulate expression of ACE2 in murine gut, decreased with an increase in the load of SARS-CoV-2 load in fecal samples from patients during the course of hospitalization (Zuo et al., 2020). It is known that *Bacteroides* strains (for example, *Bc. thetaiotaomicron*) are associated with the exogenous production of sphingolipids (for example, ceramides and deoxy-sphingolipids), and inhibition of host *de novo* synthesis of sphingolipids (Brown et al., 2019; Johnson et al., 2020). Sphingolipids are involved in defensive signaling against many viral infections. Enhanced sphingolipids possibly suppress viral replication of coronaviruses because of their role in differentiation of regulatory T (Treg) cells (Kue et al., 2013). As a result of low host *de novo* synthesis of sphingolipids, synthesis of gangliosides (binding site for coronavirus) is affected, as sphingolipids are an important part of gangliosides (Fantini et al., 2020; Kraft, 2017). Thus, *Bacteroides* supplementation as probiotics can help to combat this virus. Personalized diet and the use of supplementation containing probiotics (based on best acting probiotics) to improve the gut microbiota profile are one of the prophylactic ways which can be helpful in attenuating the fatal effects of this viral infection in immune-compromised patients and elderly people (Dhar and Mohanty, 2020; He et al., 2020; Sundararaman et al., 2020). Probiotic supplementation has also been proven effective in other coronaviruses. For instance, *Enterococcus faecium* NCIMB 10415, (Chai et al., 2013) *Lactobacillus plantarum* and *Lactobacillus salivarius* strains (Kumar et al., 2010) have been reported to inhibit transmissible gastroenteritis coronavirus.

2.2. Gut microbiota and HIV infection

There is a plethora of evidence suggesting that the gut microbiota plays a crucial role in HIV-1 pathogenesis. The prognostic significance of the gut microbiome can be estimated from the fact that epithelial barrier disruption, and innate immune activation, microbial translocation leading to inflammation predict mortality in HIV infected patients (Hunt et al., 2014). The gut microbiota is altered in case of HIV infection of an initial stage, leading to gut mucosal damage which causes depletion of CD4⁺ T cells (particularly Th17 cells) in the gut-associated lymphoid tissue, and disruption of intestinal barrier function, microbial translocation, and systemic immune activation as a result of production of inflammatory cytokines. The aforementioned mucosal events increase gut inflammation which consistently decreases CD4⁺ T cells and culminate into AIDS as microbial products are translocated from the gut lumen into the bloodstream. Even anti-retroviral therapy (ART) fails to restore altered gut microbiota and depleted CD4⁺ T cells, expressing the gut-homing receptors CCR9 and integrin $\alpha 4\beta 7$, in the gut compartment; however, CD4⁺T cells are recovered in peripheral blood (Crakes and Jiang, 2019; Mavigner et al., 2012). HIV infected patients show a perturbed gut microbiota profile regardless of sex and sexual practice. Enrichment of *Gammaproteobacteria*, and a decrease in *Ruminococcaceae* and *Lachnospiraceae*, in correlation with an increase in inflammatory markers (for example, suPAR, and nadir) and CD4⁺ count have been reported in HIV infected patients (Vujkovic-Cvijin et al., 2020)

Probiotic supplementation in HIV has shown to improve the count of CD4⁺ T cells and alleviate HIV-induced illnesses such as diarrhoea and nausea (Miller et al., 2016). Selective probiotics should be given to HIV and AIDS patients along with ART in order to protect their gut mucosal barrier and for the recovery of CD4⁺ T cells so that their life expectancy is increased (Table 1).

2.3. Gut microbiota and hepatitis

Chronic liver diseases as a result of viral infections account for a large proportion of morbidity and mortality cases worldwide and currently around 2.3 billion people in the world are infected with viral hepatitis (Jefferies et al., 2018). Approximately 150 million people in the world are infected with Hepatitis C virus (HCV); whereas about 250 million

people are chronically infected with the Hepatitis B virus (HBV) (Zeng et al., 2020). The discovery of the Hepatitis B and C viruses has revolutionized medicine and played a highly positive role in the fight against blood-borne hepatitis which affects millions of people in the world through cirrhosis and liver cancer. Two Nobel prizes have been given on the discovery of these viruses. Baruch Blumberg was awarded the Nobel Prize of 1976 in Physiology or Medicine for the discovery of HBV in 1965. Similarly, the 2020 Nobel prize in physiology or medicine has been awarded to Harvey J. Alter, Michael Houghton, and Charles M. Rice on their seminal discoveries in the last century which led to the discovery of HCV and the development of antiviral drugs.

The gut-liver axis signifies the anatomical and physiological interactions between the two organs. The hepatic portal vein, the biliary tract, and the systemic circulation are important parts of this venous system which establishes the cross-talk between the gut and liver (Konturek et al., 2018). Bile salts (200–600 mg bile acids per day) are transported from the liver to intestine and then back (95% of the bile acids) to the liver through enterohepatic circulation and they play an important role in nutrient absorption, metabolic regulation and homeostasis in both organs (Chiang, 2013). Five percent of the bile acids are changed into secondary bile acids by the gut microbiota and they are transported back to the liver through the hepatic portal veins. Thus, bile acid metabolism and the gut microbiota closely interact and modulate each other. Changes in the gut microbiota composition may also affect the host immune response to viral infection which affect the progression and development of hepatitis-related liver diseases (Yang et al., 2018). Commensals produce a variety of metabolites which have positive effects on the liver. A study showed a correlation between HBV-induced alanine aminotransferase (ALT) levels of serum and changes in gut microbiota which shows a link between liver metabolism and gut microbiota (Yun et al., 2019). Therefore, alteration in the gut microbiota has been implicated in the development and complication of liver diseases; for instance, nonalcoholic fatty liver disease and liver cirrhosis (Oh et al., 2020; Schnabl and Brenner, 2014). Cirrhosis as a result of viral hepatitis can result in altered gut microbiota profile which is characterized by a decrease in abundance of *Ruminococcus* and *Clostridium*, and an increase in the abundance of *Streptococcus*, *Staphylococcaceae*, and *Enterococcus* (Wang et al., 2019).

Association between viral infections and changes in gut microbiota has been noted in liver viral infections including the Hepatitis B and C viruses (Liu et al., 2019). Even a mild HCV infection results in perturbation of gut microbiota. An increase in *Bacteroides* and *Enterobacteriaceae* was noticed in case of HCV without any evidence of liver cirrhosis; and in the same study, a decrease in *Clostridiales* and an increase in *Lactobacillus* and *Streptococcus* (viridans streptococci) was reported in case of HCV infection of a mild stage (Inoue et al., 2018b). Some good insights were provided in another study where gut dysbiosis in hepatitis C-infected patients was noticed and characterized by a decrease in *Clostridiales* and an increase in the genera *Lactobacillus* and *Streptococcus* (Inoue et al., 2018a). When gut microbiota profile of HCV stage-4 patients was studied and compared with the gut microbiota profile of healthy patients, using high-throughput 16S rRNA gene sequencing. The alpha diversity of healthy patients was higher (more abundance of Firmicutes, Proteobacteria, and Actinobacteria) than HCV infected patients (Aly et al., 2016). Altered gut microbiota of cirrhotic HCV patients in many cases also show higher levels of endotoxin, IL-6 and TNF- α (Bajaj et al., 2016).

A significant change in the stool microbiota and serum metabolome, compared with the control subjects, of 85 chronic hepatitis B patients was noticed using the Illumina MiSeq sequencing platform. The dominant microbiota, as a result of chronic hepatitis B (CHB), in the diseased subjects had pathogenic roles in liver disease progression (Wang et al., 2017a). Chen and others provided insights into the gut microbiota profile and network changes in HCV infected patients with the progression of disease. HBV patients had higher abundance of *Haemophilus*, *Fusobacteria*, and *Veillonella* as compared to healthy subjects where

abundance of *Prevotella* and *Phascolarctobacterium* was noticed (Chen et al., 2020b). A reduction in *Bacteroides* has been observed in case of hepatitis B viral infection (Wu et al., 2012), which abundantly produce sphingolipids. Interestingly, sphingolipids have been reported to suppress replication of hepatitis B (Tatematsu et al., 2011). Liver can be further damaged by perturbation in gut microbiota due to an increase in intestinal permeability which results in the delivery of a heavy microbial antigen load, via the portal system, into the liver (Albhaisi et al., 2020; Preveden et al., 2017).

The gut lactobacilli have been reported to be helpful in protecting liver by inducing the Nrf2 antioxidant response pathway in the liver (Saeedi et al., 2020). Different approaches aiming to modulate the gut microbiota have been reported effective in HBeAg clearance. In a pilot trial, fecal microbiota transplantation (FMT), in combination with ETV/TDF therapy, in case of CHB patients showed recovery and a significant decrease in HBeAg titer after a few FMT treatments (Ren et al., 2017). Similarly, entecavir (a guanosine nucleoside analogue) treatment (ETV) was reported to significantly reduce HBeAg titer in the liver and serum in a mouse model. Caecal microbiota, especially *Akkermansia* (a gut barrier protecting bacterium) was restored following four weeks of ETV therapy (Li et al., 2020).

2.4. Gut microbiota and other viruses

Apart from the above mentioned viruses, there is a close link between many other human viruses, including enteric viruses, and the gut microbiota. Enteric viruses are primarily transmitted through the fecal-oral route and they infect the digestive tract, where they are responsible for a tremendous disease burden. Noroviruses, rotaviruses, and astroviruses (non-enveloped RNA enteric viruses) are main enteric viruses responsible for acute gastroenteritis. The relationship between gut microbiota and enteric viruses is unique in a way that commensal microbiota enhances stability and infectivity of enteric viruses.

Gut microbiota has been reported to stabilize virions in a number of ways. For instance, virus-glycan binding increases stability of virions, and infectivity of the virus is enhanced as a result of the direct interaction of glycan-bound viral particles with cellular entry receptors. Gut microbiota also modulates host immunomodulatory functions in a way that promotes virus replication (Roth et al., 2019). Many bacteria promote viral evasion and infection/ pathogenesis through their surface lipopolysaccharide, peptidoglycan (PG), and surface polysaccharides which trigger immunosuppressive pathways (Domínguez-Díaz et al., 2019). Nevertheless, several virus sensing receptors of the intestine (for example, pattern recognition receptors, cytosolic DNA sensor, toll-like receptors, and cytosolic nucleic acid sensors) sense viruses and play an important role in intestinal homeostasis and immunity (Metzger et al., 2018). The intestinal microbiota affects enteric viruses differently along the intestinal tract. Intestinal microbiota reportedly promotes the growth of enteric viruses in the distal gut; however, on the other hand, these gut commensals inhibit the replication of enteric viruses (especially noroviruses) in the proximal part of the gut due to gut-region-specific bile acid priming of type III interferon by the commensals (Grau et al., 2020). Infections caused by noroviruses may lead to other pathogenic conditions like irritable bowel syndrome (IBS), which have been shown to be linked to disrupted gut microbiota (abundance of *Escherichia coli*) in norovirus-infected patients (Nelson et al., 2012). Similar results have been obtained in a recent study showing disruption of the gut microbiota (in terms of taxonomical composition and the diversity) in children infected with either rotavirus or norovirus (Mathew et al., 2019).

Harris and others reported a difference in gut microbiota of vaccine responding infants, compared to vaccine non-responders. Rotarix™ vaccination responders showed the abundance of bacterial species belonging to *Proteobacteria*, *Clostridium* cluster XI, *E. coli* and *Serratia* (Harris et al., 2018). In a recent study, the reasons behind the disparity in the effectivity of oral rotavirus vaccine between individuals of

different countries based on socioeconomic status was found to be correlated with the nature of gut microbiota in early life (Magwira and Taylor, 2018). Similarly, another study reported that perturbation of the human gut microbiota as a result of malnutrition predisposes infants to enteric infections (Kumar et al., 2018). In an effort to determine the role of the gut microbiota in enteric infections in a trial on the Malagasy mouse lemur, it was reported that as a result of adenovirus infection, several microbial taxa important for health of the gut decreases and potential pathogens (e.g., *Neisseria*) increase (Wasimuddin Corman et al., 2019).

Apart from the commonly reported viruses, there are a number of other viral infections which result in perturbation of the gut microbiota. For instance, a clear link between the gut microbiota and some oncoviruses (cancer-causing viruses) like Human papillomavirus (HPV) and herpesviruses have been reported. HPV is mainly involved in cervical, oropharyngeal cancers, vaginal, and anal cancers. At least 600,000 new cases of cancer associated with HPV are reported every year (Arbyn et al., 2012). In a recent article, microbiota changes in HPV-induced cancers has been thoroughly reviewed (Lin et al., 2020). There are a total of 8 commonly reported herpes viruses which affect human populations, out of which herpes simplex virus HSV1 and HSV2 are the most common. Disrupted gut microbiota profile has also been reported in HSV1 (Ramakrishna et al., 2020).

3. Harnessing the gut microbiota to combat viral infections – current challenges

Unravelling temporal dynamics and genetic diversity of the human gut microbiota is crucial in understanding its link with diseases progression and control. The ecology of the gut can be engineered through microbiota-based therapeutic interventions to treat several complications related to viral infections (Fig. 1). Gut microbiota is now considered as an organ which affects the physiology of many vital organs of the body including the brain. Changes in gut microbiota pattern can also help in distinguishing diseases which are different to be distinguished by clinical practices, for instance, gut microbiota is significantly different in case of liver cancer and HBV-induced cirrhosis (Liu et al., 2019).

Therefore, it is possible to use gut microbiota patterns in clinical cases of viral infections as prognostic and predictive biomarkers in order to restore body immunity and to reduce adverse effects of viral diseases. However, it is important to consider the fact that all probiotics are not equally effective, thus a more targeted approach, rather than a blind use of traditional probiotics is recommended in any viral infection.

This aforementioned goal appears formidable because of the huge diversity of the human gut microbiota and still the least understood mutual interplay between the human gut microbiota and host health. It is no doubt that this area has huge clinical implications for several infections including almost all viral infections. Gut microbiota can be possibly manipulated in a way to develop resistance against disease. Nevertheless, the research in this area is still in its infancy and there are still more questions than answers. There is a clear link between viral infections and gut microbiota, as evidenced from thousands of studies, but causality is another debate. For instance, it remains unclear whether the disease in case of viral infections results in an altered gut microbial profile or the gut microbiota is altered due to viral infection which leads to the onset of a disease or neither of these two conditions happen. Human gut microbiota is highly malleable and it undergoes several shapes during different growth stages and under the influence of genetic factors, dietary patterns, life style, and medication. The understanding of these factors is indispensable for the exploitation of gut microbiota patterns in health and diseases. It is important to note that currently we lack a baseline or standard which should define what should a healthy gut microbiota pattern should appear like and how variations related to diet and environment may influence it, and deviation to what level will still be acceptable? Another bottleneck of the current research on human gut microbiota in relevance to health and disease is the use of germ-free

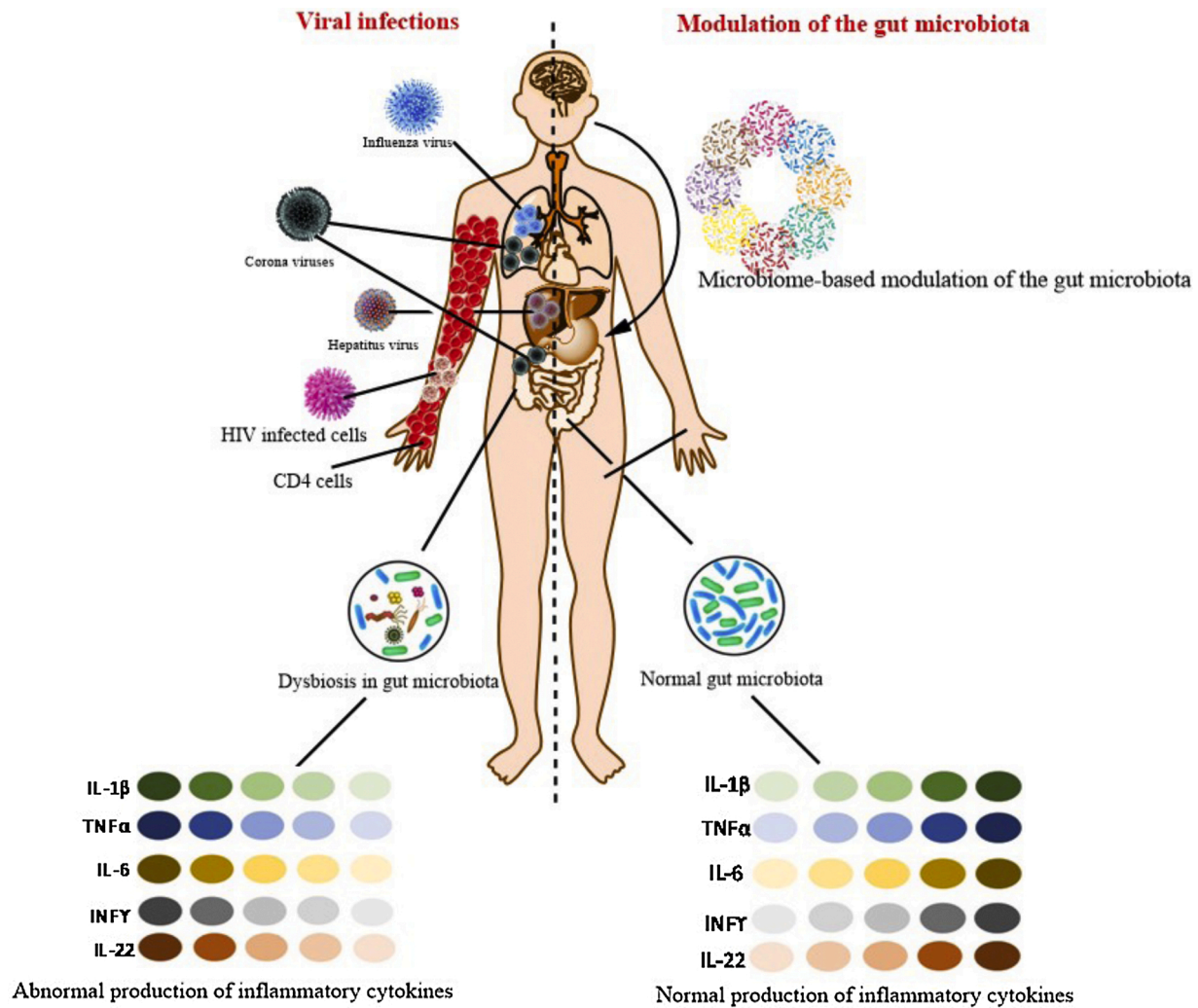


Fig. 1. Human gut microbiota dysbiosis, leading to aberrant immune response which is accompanied by abnormal production of inflammatory cytokines, following viral infections and its restoration as a result of microbiome-based therapies.

mice (gnotobiotic mice) with human microbiota being transplanted. This sounds a very useful approach, but it does not mimic microbial ecological condition in the human gut – it is pretty much similar to a sudden microbial shock in a biological environment which was totally free from microbes. Despite great anatomical and physiological similarities, there is a big difference between the natural microbiota of human and mouse. It has been reported that the human gut and mouse intestinal tract share a limited number of bacterial genera, which questions on the colonization ability of human gut microbiota into mouse (Nguyen et al., 2015). In addition, mouse cells are not susceptible to all viruses which commonly attack human cells and this further explains limitations of these *in vivo* trials.

Apart from studying variation in taxonomy of gut bacteria in disease prognosis to develop therapeutic targets, it is important to focus on microbial metabolic potential as well. The combined study of gut microbiota and metabolomics has been considered as the most promising approach to study host-microbiome interactions (Visconti et al., 2019). An ideal approach towards the exploitation of human gut microbiota for clinical trials will be to develop gut microbiota patterns and metabolomics profile of healthy and diseased subjects of different populations representing a specific geographical area, age, dietary pattern, and life style. Microbiota patterns of two individuals from different regions vary starkly depending on a combination of complex factors, some of which like genetic background are not in our hand. A number of studies have already thoroughly examined and established

microbiome of people belonging to different regions in different parts of the world, with considerations given to age, life, style, and dietary patterns (Hansen et al., 2019; Senghor et al., 2018; Zhang et al., 2019). The gut microbiota patterns of the diseased subjects can be modified in case of viral infections and other diseases using selected probiotics or FMT from healthy donors. However, it is not an easy work. Human gut microbiota is very complicated and an individual human may contain up to 1000 bacterial species and each species may have hundreds of variants in the form of strains, which remarkably differ in their characteristics. Until now, all studies have focused on gut microbiota changes at a low taxonomical level. High resolution characterization of these species at the strain level and determining their behavior and functional capacity are indispensable for microbiota-based personalized therapeutic interventions. Another challenge is the real in-depth analysis of the human gut microbiota, which, despite the non-invasiveness and convenience of fecal sampling, is not fully representative. In addition, more clinical trials are needed in the future in order to characterize functional roles of different strains in the gut and validate their role in clinical applications. However, whilst establishing links between different human populations and the role of gut bacteria in health and disease, it is not important to have the knowledge of all bacterial species or their strains. Changes in some core bacterial genera which under changes in case of viral infections may serve as markers of change, and can be termed disease-related-bacteria (DRB). The use of only some probiotic strains may bring a number of positive changes in the gut microbiome,

by increasing the abundance of some beneficial bacteria and by reducing some harmful bacteria (Hou et al., 2020).

4. Concluding remarks

Viral infections present significant public threat to health and economy throughout the world. Many viral infections result in perturbation of the gut microbiota. A plethora of evidence suggests that microbiota-based strategies have great potential to alleviate complexities associated with viral infections. For instance, the effect of sphingolipid metabolism by *Bacteroides* has a significant influence on viral pathogenesis and it should be further studied in order to develop therapeutic strategies against microbial infections. Despite all obstacles, it still remains clear that human gut bacteria have clear connection with viral infections and their evasion, and modulation of gut microbiota may provide great therapeutic options for a range of viral infections. There are still a lot of questions to be answered how to use this approach in clinical practices (see Outstanding Questions).

Some uncertainty and hype is mounting up in this field with the literature cluttering up, which involve statistically thin studies establishing connections between viral infections and gut microbiota using mice-based models; but we are sure this field has huge potential for the clinical and medicinal field, and we need to get the hype out of it in order to gather some real stuff.

5. Outstanding questions

- What is the correlation between viral infections and gut microbiota dysbiosis in terms of causality?
- How to establish standard microbiota patterns of healthy subjects of a population, since a number of complicated factors, including dietary pattern, life style, and genetics, influence the gut microbiome.
- How to determine the accurate microbiota patterns of a human, since it is well known that bacteria in fecal samples do not represent complete gastrointestinal microbiota profile.
- What other, yet to be discovered, clinical aspects of gut microbiota may be in the context of viral infections beyond the points discussed here?
- Taxonomy of all bacteria of the gut at the species and strain level cannot be inferred from currently available taxogenomics techniques, how to select specific bacterial communities that may serve as markers in different viral infections?
- What is the role of gut microbial communities other than bacteria (fungi and viruses) in different viral infections?
- What should be the best way of FMT administration for the modulation of the gut microbiota: oral ingestion colonoscopic infusion? What should be the best precautionary measures to reduce pathogens from fecal samples, especially Enterobacteriaceae and enterococci, and what levels are acceptable?

Ethics approval

Ethics approval is not applicable to this work.

Consent for publication

There is no material in the article which requires consent for publication.

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Declaration of Competing Interest

The authors have no competing interest to declare.

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