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Gut microbiota in antiviral strategy from bats to humans: a missing link in COVID-19

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Bats are a potential natural reservoir for SARS-CoV-2 virus and other viruses detrimental to humans. Accumulated evidence has shown that, in their adaptation to a flight-based lifestyle, remodeling of the gut microbiota in bats may have contributed to immune tolerance to viruses. This evidence from bats provides profound insights into the potential influence of gut microbiota in COVID-19 disease in humans. Here, we highlight recent advances in our understanding of the mechanisms by which the gut microbiota helps bats tolerate deadly viruses, and summarize the current clinical evidence on the influence of gut microbiota on the susceptibility to SARS-CoV-2 infection and risk of COVID-19 leading to a fatal outcome. In addition, we discuss the implications of gut microbiota-targeted approaches for preventing infection and reducing disease severity in COVID-19 patients.

COVID-19, SARS-CoV-2, gut microbiota, bat, anti-inflammatory, antiviral

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has been declared a public health emergency of international concern by the World Health Organization. Currently, in the face of the rapidly spreading disease and a large number of infected people, there is an urgent need for effective measures to prevent infection and avoid fatal outcomes in COVID-19. The more we learn about the novel SARS-CoV-2 virus and its associated outbreak, the better we can respond. In this context, understanding the interaction of SARS-CoV-2 with its natural host may be useful. However, the origin of SARS-CoV-2 remains unclear, although bats are currently implicated (Andersen et al., 2020; Zhou et al., 2020a; Zhou et al., 2020b). Bats are a natural reservoir for various viruses and noted for their ability to co-exist with some of the world's deadliest viruses, such as MERS-CoV, SARS-CoV, Nipah, Hendra, and Ebola viruses (Li et al., 2020c; Wang and Anderson, 2019). Via such co-existence, viral infections that are highly aggressive in humans can be persistent and avirulent in bats. Exploring the mechanism by which bats tolerate viruses can help us understand why humans are susceptible to SARS-CoV-2 and how we can co-exist with them while staying healthy, or at the very least reduce the disease severity.

Compared with humans and other mammals, bats have two unique features: tolerance to viruses and an ability to fly. What if the presence of one condition influenced the likelihood of developing the other? Previous genomic insights hinted at this connection because, via whole-genome sequencing of wild-caught bats, it was found that genes involved in minimizing DNA damage as a metabolic

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consequence of flight have been linked to immune function (Zhang et al., 2013). The increased rate of metabolism accompanying flight would lead to higher levels of oxygen-free radicals. This makes bats more prone to generating damaged DNA. Such excessive inflammation is energetically expensive and is detrimental, potentially having pathological consequences. Therefore, bats have evolved mechanisms to suppress the activation of immune responses due to damaged DNA generated by the energy used for flight, leading to reduced inflammation (Subudhi et al., 2019). Results from cell culture experiments in bats have shown that inflammation was suppressed by dampening the activation of DNA sensors, such as stimulator of interferon genes (Xie et al., 2018), and reducing levels of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) (Banerjee et al., 2017). However, the suppression of inflammation would consequently induce greater susceptibility to virus infection. The evolutionary suppression of inflammation is counteracted by the constitutive expression of innate immune genes or novel genes targeting viruses in bats, such as higher constitutive expression of interferon and interferon-stimulated genes (ISGs) (Banerjee et al., 2020). Thus, genomic insights have generated this plausible explanation for how bats may have evolved to be able to harbor such deadly viruses without experiencing disease.

In addition to the host genome, abundant evidence has shown that the microbiome in the gut directly regulates the host immune response to viral infection (Honda and Littman, 2016; Thaiss et al., 2016). However, no integrative study has yet been performed addressing whether gut microbiota contributes to bats' innate ability to act as a viral reservoir. Recently, it has been revealed that bats have a unique gut microbiota, in terms of its diversity and composition, as a consequence of physiological adaptations to flight. Is there a potential relationship among the three unique features of bats? Is it possible that the gut microbiota is the missing link between adaptation to flight and tolerance of viruses? By what mechanism does the gut microbiota help to harbor viruses, and is this pattern consistent in humans? We believe that studies of gut microbiota in bats can help to answer these important questions and more. More crucially, understanding the role of the gut microbiota in bats controlling virus-mediated pathogenesis may enable researchers to identify novel therapeutic targets to prevent and treat infections with SARS-CoV-2 in humans.

Gut microbiota: a missing link between flight and immunity in bats

Adaptation to flight structuring bats' gut microbiota

As a form of co-evolution, the adaptation of mammals to their diverse lifestyles has played a key role in structuring their gut microbiota (Rothschild et al., 2018). In bats, the adaptation to powered flight placed selective pressures on the assembly of gut microbiota. The pressure to decrease mass for more efficient powered flight reduces the microbial biomass in the gut, as it has been shown that bats carry much lower bacterial loads in the feces than nonflying mammals (Song et al., 2020a). In addition, as a by-product of selective pressure to decrease mass, bats have reduced their intestinal lengths and shortened intestinal content retention times (Caviedes-Vidal et al., 2007). Shorter guts, with correspondingly reduced anaerobic volumes, could present less of a barrier to microbial exchange through the aerobic environment. Thus, gut microbial reduction is common in bats, displaying markedly less gut microbial richness and diversity than nonflying mammals. Consistently lower resident gut microbiota might increase the proportion of transient environmental microbes relative to the total gut microbiota (Song et al., 2020a). As a result, the bats' gut microbiota consists of bacteria from their environment rather than from an evolutionary predisposition to host-specific bacteria. This is supported by evidence that the geographic locality is a strong predictor of gut microbiota composition in bats. Indeed, it has been shown that the same species of bat in five geographic localities might host five very different gut microbial communities (Lutz et al., 2019).

The discovery that adaptation to flight leads the gut microbiota of bats to be closely linked to the environment around them may suggest that bats are more highly tolerant of viruses than other mammals. In other mammals, maintaining a stable gut microbiota is achieved by eliminating invasive pathogens. However, the possession of a transient environmental gut microbiota by bats may have led to the evolution of a quite different antiviral strategy (Figure 1).

Gut microbiota in bats is linked to their unique immune responses to viruses

Bats harbor a significantly different gut microbiota composition compared with other mammals. At the phylum level, Proteobacteria overwhelmingly dominates bats' gut, followed by Firmicutes and Tenericutes, along with a few Bacteroidetes across plant- and animal-feeding bats. At the family level, the Enterobacteriaceae species in the phylum Proteobacteria are the most prevalent bacteria (Li et al., 2018). Interestingly, in humans, enrichment of Proteobacteria is a microbial signature of dysbiosis in gut microbiota, and Enterobacteriaceae is considered to be a potential pathogen (Shin et al., 2015).

Another unique microbial signature of bats is the amount of Bacteroidetes, which is significantly low in bats, but is one of the most abundant bacterial phyla in other mammals (Li et al., 2018). It is widely accepted that the gut microbial signature of high Proteobacteria and low Bacteroidetes does not

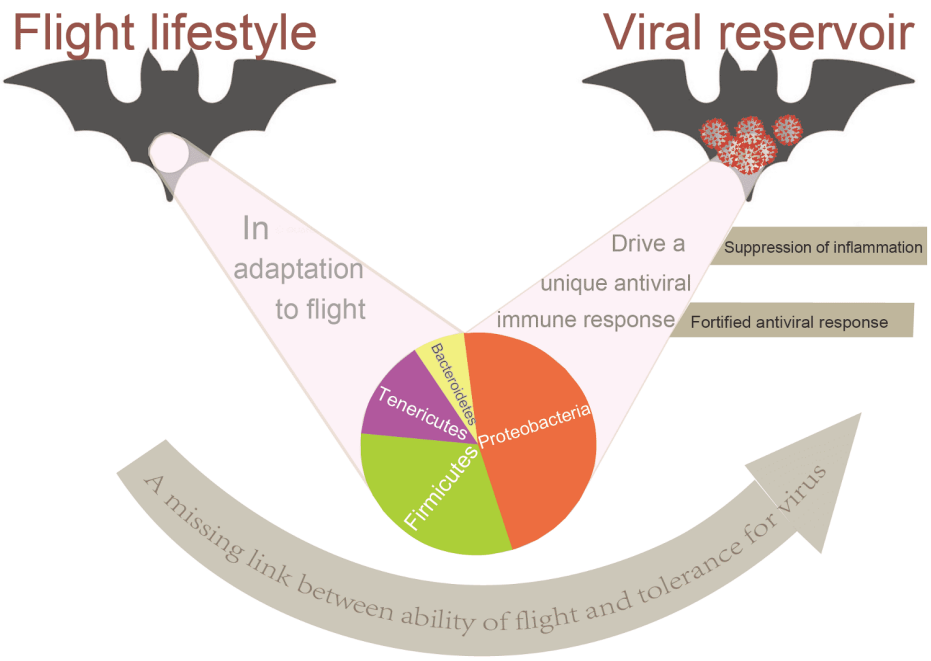

Figure 1 (Color online) Gut microbiota: a missing link between ability of flight and tolerance for virus in bats. The adaptation to powered flight of bats exerts selective pressures on the assembly of gut microbiota. The pressure to decrease mass for more efficient powered flight reduced the gut microbial biomass, displaying markedly less gut microbial richness and diversity than most nonflying mammals. Consistently lower resident microbial biomass might increase the proportion of transient environmental microbes relative to the total pool of microbes in gut. As a result, the bats' gut microbiota consist of bacteria that the bats pick up from their environment rather than from an evolutionary predisposition to host-specific bacteria, harboring a significantly different gut microbiota composition compared to other mammals. In particular, Proteobacteria overwhelmingly dominated bat guts, and was followed by Firmicutes and Tenericutes, along with a few Bacteroidetes. It has been shown that centenarians and Hadza hunter-gathers, who have a higher tolerance for Proteobacteria, have better immune resistance to inflammatory and infectious diseases. So, co-existing with a gut microbiota characterized by high Proteobacteria and low Bacteroidetes may set the basal status of immune response to virus in bats to a "tolerance status" with suppression of inflammation and fortified antiviral response, contributing to bats' innate ability to act as viral reservoir. Evidence from accumulated studies of gut microbial modifications (the germ-free animals, pathogen infection, antibiotic treatment and fecal microbiota transplantation) in bats and other mammals may support this notion.

meet the established standard parameters of a "healthy microbiota" in humans (Rinninella et al., 2019). Not only that, the gut microbial signature of bats is associated with various inflammatory diseases in humans. In both Crohn's disease and ulcerative colitis patients, the gut microbial diversity is significantly reduced, along with an increase in the phylum Proteobacteria, enrichment of the family Enterobacteriaceae, and depletion in the phylum Bacteroidetes (Eom et al., 2018; Franzosa et al., 2019). In ankylosing spondylitis patients, who often have subclinical gut inflammation or clinically defined inflammatory bowel disease (IBD), the gut microbiota is characterized by markedly decreased diversity, increased abundance of Proteobacteria, and decreased Bacteroidetes (Li et al., 2019). In addition, in cystic fibrosis patients who usually suffer from chronic gut inflammation, the predominant phylum is Proteobacteria (mainly Enterobacteriales), followed by Firmicutes and finally a few Bacteroidetes. Furthermore, probiotic intake not only significantly reduces Proteobacteria and increases Bacteroidetes, but also markedly improves gut inflammation (del Campo et al., 2014).

Interestingly, proliferation of undesirable Proteobacteria at the cost of symbiont Bacteroidetes was also found in centenarians, when compared with the young and elderly (Santoro et al., 2018). In a co-evolutionary vision of the relationship between gut microbiota and the host, centenarians who achieve healthy longevity might be those whose gut microbiota manages to continuously re-establish a mutualistic relationship with the host, adapting to the progressive endogenous and environmental changes (Biagi et al., 2017). This age-related remodeling of gut microbiota may subsequently contribute to shaping the immune status in centenarians. Previous publications have asserted that inflammation, a chronic low-grade inflammatory status, is a typical characteristic of the elderly. However, centenarians are unique in that they not only have a lower propensity to mount inflammatory responses but also exhibit efficient anti-inflammatory networks that may reduce disease severity. Therefore, the gut microbiota-driven decrease of chronic inflammation without compromising excessive inflammatory response when exposed to pathogens is the key to healthy aging and longevity (Franceschi et al., 2007).

It seems that centenarians tolerate the consolidation of a new gut microbiota ecosystem balance, resembling a property typical of the bats' gut microbiota composition. Accordingly, it is reasonable to speculate that, in adaptation to

the flight-related progressive endogenous and environmental changes, remodeling of the gut microbiota in bats may contribute to immune tolerance to viruses (Figure 1). In support of this notion, compared with Westernized populations, the Hadza hunter-gatherers, who have higher tolerance for pathogenic symbiont gut microbiota, such as members of Proteobacteria, *Succinivibrio*, and *Treponema*, are less susceptible to inflammatory and infectious diseases (Rampelli et al., 2015; Schnorr et al., 2014).

Gut microbiota driving the antiviral strategy in bats

Co-existence with a unique gut microbiota may set the basal status of immune responses to viruses to a "tolerant" status, contributing to bats' innate ability to act as viral pathogen reservoirs. One of the unique immune responses to viruses in bats is the suppression of excessive virus-induced inflammation, which has been consistently attributed to reduced expression of inflammatory cytokines, such as IL-1β and TNF-α (Banerjee et al., 2020; Subudhi et al., 2019). The ability to suppress the pro-inflammatory cytokines TNF-α and IL-1β is directly regulated by gut microbiota, which has been shown in accumulated studies of gut microbial modifications including in germ-free animals, pathogen infection, antibiotic treatment, and fecal microbiota transplantation (FMT) (Lin et al., 2019; Rosser et al., 2014; Sun et al., 2018). Additionally, the low levels of NOD-like receptor protein 3 (NLRP3) inflammasome activation in bats have been found to account for the suppression of excessive virus-induced inflammation (Ahn et al., 2019). However, the extent to which NLRP3 signaling is activated appears to be greatly influenced by the composition and function of the gut microbiota (Seo et al., 2015; Singh et al., 2019). To act as a viral reservoir, the defect of suppressed inflammation is counteracted by a more efficient antiviral defense system to target viruses in bats. Studies have shown that interferon (IFN) and interferon-stimulated genes (ISGs) were constitutively expressed at higher levels in bats than in other mammals (Hölzer et al., 2019; Zhou et al., 2016), which suppressed viruses down to levels of persistence. The gut microbiota is considered to be involved in regulating bats' fortified antiviral defenses (Figure 1). Results from antibiotic treatment and fecal transplantation demonstrated that the gut microbiota can act at multiple levels to enhance antiviral resistance. This process includes increasing IFN production and ISG induction in the lungs to control viral infection early on, and enhancing the functionality of immune cells leading to improved innate and adaptive immunity later in viral infection (Bradley et al., 2019; Steed et al., 2017).

Although this is indirect evidence, studies of gut microbial modifications in bats would provide further support for the role of gut microbiota in bats' unique antiviral responses. Previous studies in bats showed that diet and pathogenic infection induced changes in gut microbiota composition in a way that could have an impact on immune responses to viruses. Consuming blood is an extreme evolutionary specialization, as blood is a nutrient-poor resource that is low in carbohydrates and vitamins. The common vampire bat (*Desmodus rotundus*) is one of only three mammalian species that feed exclusively on blood. Evidence has shown that this dietary specialization may cause vampire bats to have a gut microbiota harboring more pathogenic bacterial species, contributing to a more efficient immune system for antiviral defense (Zepeda Mendoza et al., 2018). Another study further elucidated how dietary changes in *Desmodus rotundus* influenced its immune response to viral infection. Results revealed that, compared with feeding on blood of wild animals in a forest fragment, bats feeding on blood of livestock showed changes in the relative abundance of several core bacterial taxa, which may decrease immune resistance to viral infection (Ingala et al., 2019). In a pathogenic infection model, it has been revealed that infection with astrovirus induced a higher pathobiont-like shift in the gut microbiota of young compared with adult bats. This different change in gut microbiota composition between young and adult bats was suggested to be responsible for their distinct immune responses to infection, as adult bats have a better immune defense against astrovirus infection and other enteric pathogens, whereas young bats often develop an increased severity of disease after infection (Wasimuddin et al., 2018).

Findings from bats: implications for COVID-19 crisis

Hosts and their own unique gut microbiota achieve co-existence over a long history of mutualistic symbiosis, in which gut microbiota has the potential to promote the host's health and provide defenses against invading pathogens. What we learn from bats is that harboring gut microbiota with a microbial signature of dysbiosis in humans is responsible for the suppression of inflammation and fortified antiviral responses, contributing to deadly virus defense and reduction of disease severity. This information from the natural host of SARS-CoV-2 highlights the potential importance of gut microbiota in SARS-CoV-2 infection and disease progression in humans. As such, the gut microbiota can be explored for potential natural defenses against a fatal outcome of COVID-19 in humans.

Involvement of gut microbiota in COVID-19

The COVID-19 pandemic has rapidly spread all over the world. The virus most likely infects respiratory epithelial cells and spreads mainly via the respiratory tract from human to human, as the viral infection causes a series of respiratory

illnesses including severe respiratory syndrome (Mu et al., 2020). However, recent publications have suggested that the value of intestinal immunity and gut microbiota may be underestimated in COVID-19. In support of this, clinical observations showed that the viral receptor angiotensin-converting enzyme 2 (ACE2) used by SARS-CoV-2 for the entry process is highly expressed in the gut and linked to intestinal inflammation (Hashimoto et al., 2012; Letko et al., 2020; Xiao et al., 2020), and approximately 10% of patients with SARS-CoV-2 infection present diarrhea (Song et al., 2020b). In addition, COVID-19 patients showed gut microbial dysbiosis with reduced diversity, a significantly increased relative abundance of opportunistic pathogens, and a decreased abundance of beneficial symbionts, such as *Lactobacillus* and *Bifidobacterium* (Silan Gu et al., 2020; Xu K et al., 2020; Zuo et al., 2020c). Furthermore, serial studies recently provided convincing evidence supporting the involvement of the gut microbiota in intestinal SARS-CoV-2 infection, as it was reported that SARS-CoV-2 RNA was detected in stool samples (Yeo et al., 2020), active SARS-CoV-2 replication was observed in human intestinal epithelial cells and COVID-19 patients' intestinal tissue (Qian et al., 2020; Stanifer et al., 2020), as well as SARS-CoV-2 intestinal viral activity being associated with gut microbiota composition in COVID-19 patients (Zuo et al., 2020a). These publications may suggest that there is interplay between intestinal SARS-CoV-2 and the gut microbiota in COVID-19 patients. Evidence has shown that a lack of ACE2 led to obvious alteration in the gut microbiota composition in mice, which resulted from reduced production of the antimicrobial peptides that control the gut microbial community (Hashimoto et al., 2012). Moreover, loss of ACE2 during pulmonary hypertension is associated with gut microbiota dysbiosis in humans (Kim et al., 2020). It seems that SARS-CoV-2 infection induced reduction of ACE2 can lead to alteration in the composition of the gut microbiota. In parallel with this, alterations in gut microbiota may influence the intestinal SARS-CoV-2 activity. Recent studies have reported that Bacteroides species, which downregulated ACE2 expression in murine gut, correlated inversely with intestinal SARS-CoV-2 load in COVID-19 patients (Zuo et al., 2020c). However, there is a need for further studies to determine the role of the gut microbiota in intestinal SARS-CoV-2 activity, which should be investigated in relevant animal models of COVID-19 by performing fecal transfer experiments. Possible models include non-human primates, ferrets, human-ACE2-expressing mice, and hamsters (Callaway, 2020).

Following intestinal SARS-CoV-2 infection, the altered gut microbiota may then regulate the gastrointestinal symptoms in COVID-19 patients. It has been shown that the ACE2-mediated intestinal inflammation was greatly influenced by the composition and function of the gut microbiota, as transplantation of the altered gut microbiota from *Ace2* mutant mice into germ-free wild-type hosts was able to transmit a highly increased propensity to develop severe colitis (Hashimoto et al., 2012).

Intriguingly, compared with a profile showing high expression of ACE2 in the human gut, the expression of ACE2 was quite low in lung tissues from healthy donors (Liang et al., 2020). This significant difference has raised concerns about the pathological importance of gut microbiota in lung infection with SARS-CoV-2 and the subsequent severe respiratory syndrome. Indeed, a recent report demonstrated that alterations in gut microbiota of patients with SARS-CoV-2 infection were associated with the severity of COVID-19 respiratory disease (Zuo et al., 2020c). However, how can microbiota in the gut communicate with the lungs from a distance? Emerging experimental and epidemiological evidence highlights crucial cross-talk between the gut microbiota and the lungs, termed the gut–lung axis, which includes several pathways (Figure 2). (1) The mesenteric lymphatic system pathway is an essential pathway between the gut and the lungs, through which the gut microbiota-derived components and metabolites, such as short-chain fatty acids (SCFAs), may translocate across the intestinal barrier, reach the systemic circulation, and modulate the lung immune response (McAleer and Kolls, 2018). (2) While SCFAs have direct effects on the lungs, they also alter lung health through changes in bone marrow hematopoiesis. Many innate and adaptive immune cells that populate the lungs originate in the bone marrow. Thus, SCFAs can shape and promote bone marrow hematopoiesis to resolve pulmonary inflammation and to support healthy homeostasis (Trompette et al., 2014). (3) The gut is also a source of immune cells for the lungs. The innate lymphoid cells that are involved in tissue repair have been shown to be recruited from the gut to the lungs in response to inflammatory signals in the presence of IL-25 (Huang et al., 2018). (4) Gut microbiota can enhance IFN production and ISG induction in the lungs to increase antiviral resistance to viral infection (Bradley et al., 2019). (5) Gut microbiota can influence pulmonary microbial composition by both direct seeding of the respiratory tract with bacteria and the distribution of bacterial metabolites, such as SCFAs, which promote the growth of certain SCFA-producing bacteria (Marsland et al., 2015).

Clinical reports have shown that COVID-19 affects not only the respiratory and gastrointestinal systems, but also the central nervous system. Indeed, neurological manifestations related to COVID-19 have been addressed in large studies. The specific neurological symptoms in COVID-19 patients normally include acute cerebrovascular disease, ataxia, seizure, cranial nerve involvement, and neuroinflammation-associated neurological disorders (Asadi-Pooya and Simani, 2020; Beyrouti et al., 2020; Kempuraj et al., 2020). In addition to direct CNS invasion, microthrombosis, severe hypoxemia, and neurological side effects of antiviral

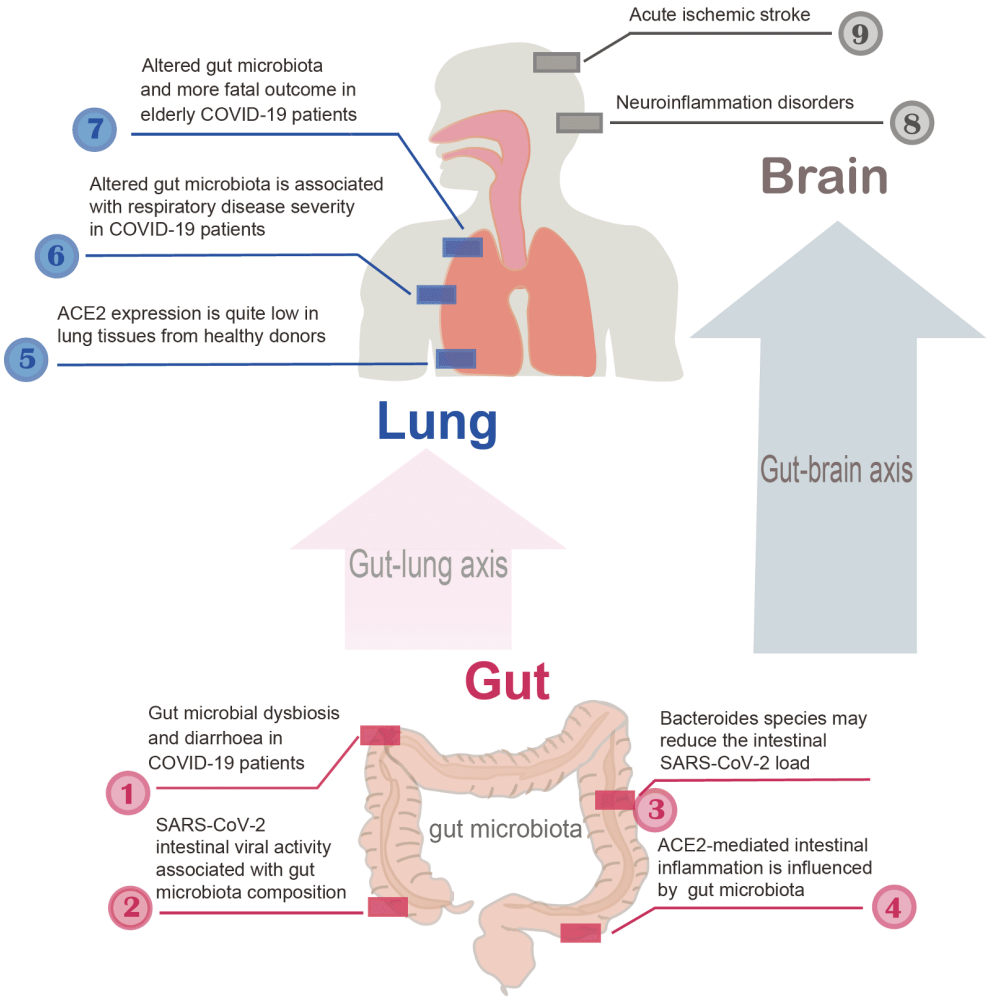

Figure 2 (Color online) The potential influence of gut microbiota on COVID-19 disease outcome. Gut micorbiota is associated with intestinal SARS-CoV-2 infection and plays a vital role in gastrointestinal symptom (①–④) of COVID-19. Subsequently, the influence of gut microbiota reaches the lung and brain through the gut–lung axis and gut–brain axis respectively, contributing to respiratory disease severity (⑤–⑦) and neurological manifestations in COVID-19 (⑧–⑨).

medications, the mechanism of gut microbial dysbiosis has been proposed to explain the neurological damage produced by COVID-19 (Sultana and Ananthapur, 2020; Whittaker et al., 2020). Alteration of the composition of the gut microbiota during intestinal SARS-CoV-2 infection could be involved in the pathogenesis of neuropsychiatric symptoms via the gut–brain axis, including the immunological, hormonal, and neuronal pathways. A large number of studies have shown that the gut microbiota can affect various neurological symptoms and mental functions, such as anxiety, depression, multiple sclerosis, seizure, Parkinson's disease, autism, and Alzheimer's disease (Cryan et al., 2019).

There is now a growing body of evidence about how gut microbial dysbiosis negatively impacts neurological manifestations in COVID-19 patients. It has been reported that the neurological manifestations normally have a higher incidence in patients with a more severe course of COVID-19 (Chen et al., 2020). As reported in elderly and critically ill COVID-19 patients, their altered gut microbiota contributes to the IL-6-mediated cytokine storm (Thevaranjan et al., 2017), which influences the extent of acute respiratory distress syndrome, the pathogenesis of neuroinflammation, and other neurological disorders (Kempuraj et al., 2020; Muccioli et al., 2020). Therefore, the gut microbial dysbiosis in COVID-19 could modulate the neurological manifestations via the immunological pathway of the gut–brain axis. This is well described in acute ischemic stroke and neuroinflammatory disorders (Figure 2). In a recent paper, the gut microbiota has been described to regulate the onset of acute ischemic stroke through the immunological pathway (Battaglini et al., 2020). In respect to neuroinflammatory disorders, recent reports have revealed that COVID-19 might represent a risk factor for Parkinson's disease (PD). Previous studies have suggested that the pathogenesis of PD is strongly associated with gut microbial dysbiosis and colon inflammation. Indeed, several lines of evidence support the hypothesis that PD first begins in the gut and then spreads to the CNS (Sampson et al., 2016; Yang et al., 2019). As de-

scribed earlier, significantly altered gut microbiota composition was observed in COVID-19 patients, and gut microbial dysbiosis was found to contribute to the IL-6-mediated cytokine storm. This increase in pro-inflammatory cytokines may then compromise intestinal barrier integrity, causing elevation of circulating lipopolysaccharides (LPS), which might eventually trigger microglial activation and neuroinflammation. Additionally, the gut microbial dysbiosis may modulate the symptoms of PD in COVID-19 patients via the neuronal pathway of the gut–brain axis. One histopathological hallmark of PD is the intraneuronal accumulation of aggregates of the protein α-synuclein (aSyn). In this respect, gut microbial dysbiosis-mediated LPS elevation can stimulate the formation of aSyn in enteric nerves, which occurs prior to the onset of motor symptoms. In support of this, treatment with a specific gut bacterium that is markedly increased in PD mouse models was found to be sufficient to provoke the selective death of dopamine neurons and motor deficits in mice, accompanied by neuroinflammation and accumulation of aSyn in both colon and brain (Follmer, 2020). Although it is mechanistically feasible that the gut microbiota is involved in the pathogenesis of neuropsychiatric symptoms in COVID-19 infection via the gut–brain axis, the role of gut microbial dysbiosis in this setting remains to be investigated in clinical studies.

The role of gut microbiota in increased risk for severe COVID-19

The spread of COVID-19 throughout the world has been a severe challenge for public health. There is an urgent need to explore the essential reasons for the susceptibility to SARS-CoV-2 infection and increased risk for a severe COVID-19 outcome. According to the important influence of the gut microbiota in COVID-19 infection and disease outcome, we propose that the disruption of gut microbial homeostasis may lead to an increased infection risk and poor outcome of COVID-19.

The gut microbial homeostasis of modern urban residents has been significantly perturbed by dramatic changes in the diet and lifestyle, increased antibiotic use, and excessive hygiene (Hills et al., 2019). For instance, urban residents typically consume a high-fat and high-refined-carbohydrate diet, which is rich in sucrose and fructose but lacks dietary fiber, perturbing the gut microbiota (Tomova et al., 2019). In addition, significantly reduced physical activity and disrupted circadian rhythm could also disrupt the gut microbiota (Matenchuk et al., 2020; O'Sullivan et al., 2015). In comparison, dwellers in remote rural areas who often have a traditional lifestyle maintain gut microbial homeostasis. It has been shown that, compared with rural African children in an environment that still resembles that of Neolithic subsistence farmers, Western European children have reduced gut microbial diversity and gut microbial dysbiosis associated with inflammatory diseases (De Filippo et al., 2010). This perturbed composition of the gut microbiota may contribute to the increased risk of respiratory tract infection as well as inflammatory diseases. Global comparisons revealed that lifestyle practices, such as caesarian section and antibiotic use, reduced the diversity and altered the composition of the gut microbiota, leading to a predisposition to asthma and an increased risk of respiratory virus infection and more severe disease outcomes (Shao et al., 2019).

It is noteworthy that people with more risk factors disrupting the homeostasis of the gut microbiota may have increased susceptibility to SARS-CoV-2 infection and risk of developing severe and fatal COVID-19. Thus, we propose that more attention should be paid to individuals with gut microbial dysbiosis during the COVID-19 outbreak. A special focus on this issue may help us better understand why some patients are completely asymptomatic, some develop mild symptoms, while others suffer acute respiratory distress syndrome. Accordingly, more insight into the pathological importance of the gut microbiota in the elderly should be obtained, since studies have shown that patients aged 65 years and older have an increased risk for SARS-CoV-2 infection and higher mortality of COVID-19 pneumonia (Du et al., 2020; Yuan et al., 2020). This increased risk in the elderly is not due to enriched ACE2 receptor expression, which is a prime target for the pathogenesis of COVID-19 (Li et al., 2020b). In fact, ACE2 expression has been shown to be dramatically reduced in the lungs of the elderly (Al-Ghatrif et al., 2020). However, compared with young adults, the elderly are known to have an altered composition of the gut microbiota. A number of studies have shown that a significant drop in diversity and decreased abundance of beneficial bacterial species are accompanied by the outgrowth of pathogenic species in the gut microbiota of the elderly. In terms of more specific details at the genus and family levels, Firmicutes and Actinobacteria (mainly *Bifidobacteria*) were found to be decreased, whereas Bacteroidetes and Proteobacteria (especially Enterobacteriaceae) were increased in the elderly (O'Toole PW and IB., 2015; Odamaki et al., 2016). Interestingly, the alteration in gut microbiota in the elderly is similar to the changes induced by antibiotic treatment, although both drug-related factors (such as antibiotic class, timing of exposure, or route of administration) and host-related factors (such as age at exposure) influence the alterations of gut microbiota produced by antibiotics. Based on results from different studies, antibiotic treatment was shown to result in a reduction in total bacterial diversity, and decreases of Firmicutes (mainly *Lactobacilli*) and Actinobacteria (especially *Bifidobacteriaceae* and *Bifidobacteria*), but an increase in Bacteroidetes and Proteobacteria (particularly Enterobacteriaceae) (Francino, 2016; Ianiro et al., 2016).

As described earlier, antibiotic treatment that disrupts the gut microbiota results in significantly reduced immune responses against influenza virus and a worse outcome in pulmonary infection. Therefore, it is reasonable to speculate that the altered composition of the gut microbiota in the elderly may contribute to a higher risk for severe COVID-19 (Figure 2). Mechanistically, the cause of mortality in viral SARS-CoV-2 pneumonia is uncontrolled inflammation, whereby a large number of immune cells and substantial tissue fluid in the lung can block gas exchange between the alveoli and capillaries, leading to acute respiratory distress syndrome. It has been found that a rapid increase in the pro-inflammatory cytokine IL-6 plays a key role in the formation of this lethal cytokine storm (Chen and Zhong, 2020). According to animal and human studies, aged gut microbiota can cause higher IL-6 and peribronchiolar cellular infiltration in the lungs in the absence of stimulation or overt infection, increasing the risk for a fatal outcome of COVID-19 (Fransen et al., 2017; Thevaranjan et al., 2017).

These results suggest the potential value of the gut microbiota as a diagnostic biomarker for COVID-19. Indeed, several studies have shown that patients with chronic kidney disease, type 2 diabetes, hypertension, obesity, and non-alcoholic fatty liver disease, who had gut microbial dysbiosis, were at a higher risk of, and mortality from, COVID-19 infection (Bornstein et al., 2020; Fang et al., 2020; Finer et al., 2020; Henry and Lippi, 2020; Prins and Olinga, 2020). Although the increased risk in these conditions may be partly due to the increased ACE2 expression and treatment with ACE inhibitors, which result in upregulation of ACE2 (Fang et al., 2020), the specific composition of the gut microbiota linked to a severe COVID-19 outcome still needs to be addressed.

Gut microbiota as a potential target against COVID-19

On account of the importance of the gut microbiota in the susceptibility to SARS-CoV-2 infection and the risk of a fatal COVID-19 outcome, it is suggested that the gut microbiota may be able to act as a therapeutic target against COVID-19. What we know from bats is that the maintenance of gut microbial homeostasis with a high tolerance for pathogenic symbiont gut microbiota, such as members of Proteobacteria, may contribute to a marked reduction in disease severity of viral infection. This may suggest that the establishment of a mutualistic symbiotic relationship with Proteobacteria may avoid poor outcomes in COVID-19, as centenarians and Hadza hunter-gatherers, who have higher tolerance for Proteobacteria, have better immune resistance to inflammatory and infectious diseases. However, intolerance to members of the Proteobacteria may lead to various inflammatory diseases and an increased risk of viral infection in humans. In mammals, it has been widely recognized that exposure to specific microbes early in life plays an instrumental role in facilitating tolerance to the gut microbiota, which subsequently has long-lasting consequences for the immune response that extend into adulthood (Gensollen et al., 2016). Exposure to microbiota during early childhood contributes to the suppression of excessive inflammatory responses in adulthood, which is supported by the fact that early-life microbial exposure is associated with protection from inflammatory diseases such as IBD and asthma. In contrast, exposure to antibiotics in childhood, especially during the first year of life, was found to be associated with an increased risk for developing IBD, in which basal expression levels of the inflammatory cytokines were increased (Torres and Peter, 2019). Therefore, exposure to Proteobacteria early in life may facilitate the establishment of a mutualistic symbiotic relationship with Proteobacteria and subsequent reduction in disease severity upon viral infection. This may suggest that individuals growing up in Proteobacteria-rich environments would have a reduced risk of COVID-19. One of the environments dominated by Proteobacteria is a soil-rich natural environment, as frequently encountered by those in rural areas. This may provide an explanation for why urban residents growing up in environments with degraded soil have markedly less tolerance to Proteobacteria, a higher risk of inflammatory diseases, and increased risk of viral infection, compared with residents in rural areas (Tasnim et al., 2017). Besides a high tolerance for Proteobacteria, increased gut microbiota diversity and enriched abundance of beneficial bacterial species have also been shown to enhance the immune defense against viral infection in bats (Wasimuddin et al., 2018). Consistent with this, in humans, the enriched gut microbial diversity and beneficial species are responsible for the anti-inflammatory response and antiviral response (Uchiyama et al., 2019). Early exposure to a soil-rich natural environment has also been shown to increase gut microbiota diversity and beneficial microbes, and consequently enhance innate immunity and reduce respiratory tract infection of viral origin (Blum et al., 2019). Therefore, exposure to soil-rich natural environments early in life may be useful to reduce the infection risk and avoid poor outcomes from COVID-19. Although it is mechanistically feasible, the role of early-life exposure to soil-rich natural environments in this setting has yet to be investigated in preclinical and clinical trials.

Early-life exposure to microbes may be vitally important, determining specific immune events that are durably imprinted into adulthood. With the progressive stabilization into an adult-like community structure throughout adulthood, the gut microbiota also plays an essential role in regulating immune responses to pathogenic viruses. For adults, specific gut microbiota-targeted approaches can be selected to increase the gut microbiota diversity and beneficial bacterial species. At present, the main examples of these gut

microbiota-targeted approaches include FMT, probiotic supplementation, and the intake of products favoring the growth of beneficial bacteria and metabolite production, such as prebiotics and a Mediterranean-like diet (Figure 3).

Diet is the factor most strongly influencing the structure of the gut microbiota, exerting its influence throughout the lifespan. Published studies have consistently shown the ability of specific diets and dietary factors, mostly a Mediterranean-like diet loaded with fermented food, dietary fibers, polyphenols, carotenoids, omega-3 polyunsaturated fatty acids, and unsaturated fatty acids, to preserve lung function and health (Scoditti et al., 2019). By contrast, a Western diet, rich in refined grains, desserts, sweets, sweetened beverages, saturated fat, cured meats (such as bacon, hot dogs, and processed meats), and red meats, is associated with impaired lung function and the risk of chronic ob-

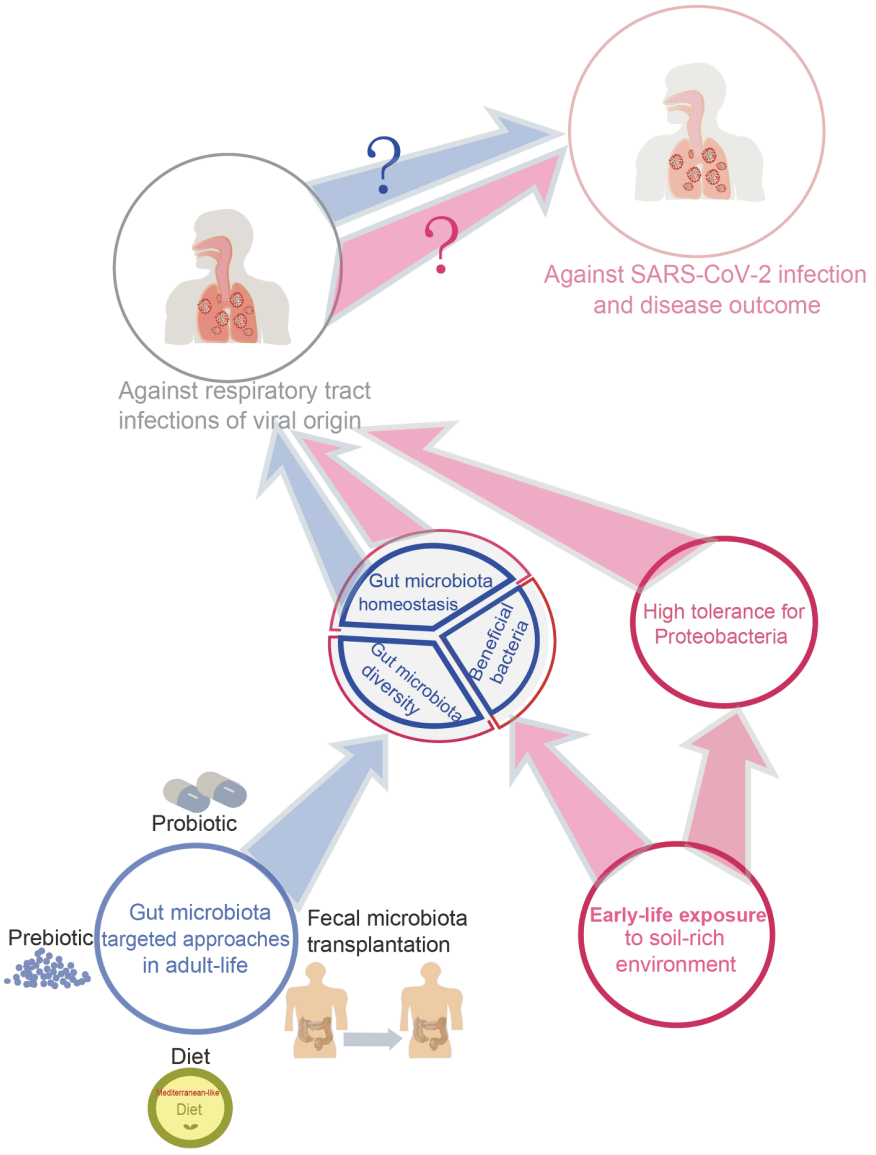

Figure 3 (Color online) Gut microbiota as a potential target against COVID-19. As exposure to specific microbes in early life plays an instrumental role in facilitating tolerance to their gut microbiota and following durable consequences for the immune response that extends into adult life, exposure to Proteobacteria in early life may promote a high tolerance for Proteobacteria (microbial signature of bats, centenarians and Hadza hunter-gathers) and following reduction in disease severity of viral infection. One of the environments dominated by Proteobacteria is the soil-rich natural environment. Moreover, early-life exposure to soil-rich natural environments maintains the gut microbiota homeostasis, increases the gut microbiota diversity and beneficial bacterial species, enhancing the immune defense to viral infection. In spite of the vital importance of early-life microbial exposures in determining specific immune events that are durably imprinted in adult life, the gut microbiota in adulthood also takes an essential part in regulating immune response to pathogenic virus. For adults, they can choose specific gut microbiota targeted approaches to maintain gut microbiota homeostasis, and increase the gut microbiota diversity and beneficial bacteria. These gut microbiota targeted approaches mainly include fecal microbiota transplantation (FMT), probiotic supplement and intake of products favoring the growth of beneficial bacteria and metabolite production, such as prebiotics and Mediterranean-like diets. Although the early-life exposure to soil-rich natural environments and these gut microbiota targeted approaches have a promising potential against respiratory tract infections of viral origin, the rationale for using them in COVID-19 is derived from indirect evidence, so their effect needs to be determined in future well-designed preclinical and clinical studies.

structive pulmonary disease (Kaluza et al., 2019). Findings indicated that a Mediterranean diet improved lung health through eliciting favorable microbiota profiles and metabolite production, while a Western diet induced dysbiosis in gut microbiota composition, leading to elevated airway inflammation and reduced immune response against viral infection (Gentile and Weir, 2018). Among the Mediterranean-like dietary factors, the dietary fibers can be fermented by gut microbiota to product SCFAs. SCFAs contribute to maintaining a healthy gut microbiota composition, and act on the gut–lung axis to promote lung health, including attenuating the inflammatory and allergic responses in the lungs, as well as enhancing the immune defense against respiratory viral infection (Dang and Marsland, 2019; Lewis et al., 2019). Besides the potential benefit of reducing the risk of SARS-CoV-2 infection, SCFAs may also play a role in preventing pathogenic superinfection during SARS-CoV-2 infection. According to recent publications, alteration in the production of SCFAs by the gut microbiota increased susceptibility to secondary bacterial pneumonia in patients infected with the H7N9 influenza virus, while supplementation with SCFAs acetate reduced bacterial superinfection and lung pathology (Sencio et al., 2020). Bacterial superinfections can occur in the aftermath of viral infection and contribute significantly to the excess morbidity and mortality, as shown in influenza. In terms of COVID-19, the primary outcome measure is respiratory failure; the secondary outcome measure is the occurrence of bacterial superinfection among ventilated patients with SARS-CoV-2 pneumonia.

Prebiotics are non-digestible food ingredients that selectively stimulate the growth and activity of probiotics to improve host health. They mainly include oligosaccharides, unsaturated fatty acids, dietary fibers, and polyphenols (Gibson et al., 2017). Evidence suggests that, by improving the function of the microbiota–gut–lung axis, prebiotics can prevent respiratory diseases including respiratory tract infections, lung cancer, asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, and acute lung injury (Huang et al., 2019; Langlois et al., 2019; Pizzini et al., 2018). Crucially, prebiotics, a high-fiber diet, and probiotics may have the potential to reduce the risk of severe symptoms in diabetic patients infected with SARS-CoV-2. Depending on the geographic region, 20%–50% of patients in the COVID-19 pandemic had diabetes. These patients have an increased risk of severe complications including respiratory distress syndrome and multi-organ failure, which may be attributable to high glucose levels (Bornstein et al., 2020). Coincidentally, high glucose levels may also explain why some patients with influenza infection have worse symptoms than others (Wang et al., 2020). Accumulated studies have demonstrated that prebiotics, dietary fiber, and probiotics can regulate glycometabolism by improving glucose control and insulin sensitivity (Anhê et al., 2015; Cooper et al., 2017; Li et al., 2017).

The most commonly used probiotics are *Lactobacillus* and *Bifidobacterium* species. A number of animal and clinical studies have recently been reported that corroborate the effect of different probiotic strains to ameliorate or prevent viral infections, such as decreasing titers of Ebola and cytomegalovirus, and reduced duration and severity of respiratory tract infection caused by respiratory or influenza viruses (Dumas et al., 2018; Kanauchi et al., 2018; Kiousi et al., 2019). For instance, one study revealed that *Lactobacillus gasseri* can protect against respiratory syncytial virus infection in mice, as the RSV titer and expression of pro-inflammatory cytokines in the lungs were significantly decreased, while IFN and ISGs were upregulated after the treatment (Eguchi et al., 2019). With regard to clinical trials, probiotic consumption has been shown to be effective at reducing the severity and duration of respiratory tract infections and increasing the immune defense against influenza in children (Laursen and Hojsak, 2018; Wang et al., 2016) adults, and the elderly (Lehtoranta et al., 2014). However, it should be noted that the beneficial effects of probiotics on the outcome of respiratory tract infections may be dependent on the use of different probiotic strains, bacterial dose, and the matrices used.

Fecal microbiota transplantation (FMT) is the process by which fecal microbiota is transplanted from a healthy donor to the recipient's gut in order to recover gut microbial homeostasis. It has been effectively used in the treatment of various diseases including recurrent *Clostridium difficile* infection, IBD, IBS, and obesity (Wortelboer et al., 2019). Remodeling the gut microbiota through FMT not only recovers gastrointestinal function, but is also effective at treating respiratory tract diseases. The latest research has indicated that FMT can be beneficial at relieving respiratory tract inflammation, ameliorating viral and bacterial infection (Jagessar et al., 2019; Laffin et al., 2017), and improving endotoxic acute lung injury (Li et al., 2020a).

The above data suggest that probiotic supplementation and FMT have potential for use against respiratory tract infections of viral origin. However, no reported studies have yet evaluated the use of probiotics and FMT as add-on therapy for COVID-19. Similarly, at present, there is only indirect evidence supporting the use of dietary fiber and prebiotics as daily supplements in the personalized diet in COVID-19 patients. Therefore, the application of these gut microbiota-targeted approaches to reduce infection and improve clinical outcomes of COVID-19 need further support from evidence from preclinical and clinical trials (Figure 3).

Conclusion

Mammals have evolved in a microbial world, so gut mi-

crobial symbionts have played a vital role in antiviral defense to promote host health. The antiviral role of gut microbiota has been well studied in the laboratory. To date, the majority of such studies have focused on laboratory mouse models, being confined to highly sterile environments, which is not representative of the complexity of gut microbiota present in wild hosts and results in altered immune development (Rosshart et al., 2019). Thus, these laboratory studies have left broad patterns of gut microbial function and natural immune response to viruses unclear. In gut microbiota research, there is an urgent need for a wildlife model system. Bats are unique among mammals as the only ones capable of hosting and co-existing with various viruses, including some of the world's deadliest viruses and those that infect humans. We propose that bats represent a model system ideal for comparative microbiome research for human infectious disease of viral origin, which can help us answer key questions about viral tolerance and disease outcome. In addition, bats include an abundance of species and enjoy a cosmopolitan global distribution, with nearly 1,400 described species, constituting approximately 20% of all living mammals, and being found on every continent save Antarctica. As a highly diverse and ecologically important mammal, bats are a good system within which to attempt to answer new questions about the gut microbiota-driven virus–host coevolutionary trajectory.

In its adaptation to a flight-based lifestyle, the unique gut microbial composition profoundly contributes to bats' status as a viral reservoir. In future studies, there is a need to clarify the molecular pathways by which this special gut microbiota influences the tolerance of bats to viruses and the species-based or community-based effects. It is clear that such studies will shed light on how the gut microbiota impacts on infectious disease susceptibility and outcome in bats and humans. For instance, since the gut microbiota of bats is more closely linked to their living habitats, more attention should be paid to the possibility that human-caused disturbances to bats' habitat may perturb their gut microbiota, such as by destroying their immune defense against white nose syndrome, which has ravaged bat colonies all over the world. As for humans, advances in our understanding of bat–microbe mutualism may highlight how to avoid severe disease outcomes in SARS-CoV-2 infection.

Given the importance of gut microbiota in immune defense against viral infection, there is a need for caution to avoid unnecessary antibiotic treatments. With significant adverse effects on gut microbiota homeostasis and diversity, increased antibiotic use may have the unintended and devastating consequence of increasing the risk for SARS-CoV-2 infection and severe disease outcome. However, in China, 58%–71% of COVID-19 patients were given antibiotics, and diarrhea occurred in 2%–36% of patients (Guan et al., 2020; Wong et al., 2020). Hopefully, the application of these findings in a clinical context is approaching. When antibiotics are used in COVID-19 patients, the re-establishment of gut microbiota homeostasis by probiotic supplementation to reduce infection and fatal outcome has been proposed globally. China's National Health Commission and National Administration of Traditional Chinese Medicine have suggested the use of probiotics in patients with severe COVID-19. In the United Kingdom, an ongoing Phase II randomized, double-blind, placebo-controlled trial is evaluating the efficacy and safety of oral live biotherapeutic MRx-4DP0004 in addition to standard supportive care for hospitalized COVID-19 patients. In the USA, a multicenter, Phase II randomized, double-blind, placebo-controlled trial is being conducted to evaluate the ability of a commercial product of *Lactobacillus rhamnosus* GG to decrease infection and improve outcome in COVID-19 patients (Akour, 2020).

Besides highlighting the gut microbiota *per se* in COVID-19, future studies may also explore the effect of microbiota-derived metabolites, such as fatty acids, neural signals, and polyamines. Among these, SCFAs have emerged as key signaling molecules within the gut and in the periphery to limit inflammation and enhance protective responses to viral infection. Second, further studies should clarify whether the lung microbiota is involved in COVID-19. Cross-talk between the gut and lung microbiota has been proposed, as it showed that changes at one of these two sites could impact the other. Finally, it would be interesting to dissect the role of other gut microorganisms such as fungi and other viruses in COVID-19. In fact, fungi and viruses form an important niche ecosystem in the gut, which respectively constitute the gut mycobiome and the gut virome. A recent report showed that COVID-19 patients had significant alterations in their fecal mycobiome compared with controls, characterized by enrichment of *Candida albicans* and a highly heterogeneous mycobiome configuration, at the time of hospitalization, which persisted in a subset of patients for up to 12 days after nasopharyngeal clearance of SARS-CoV-2. However, the contributions of an altered gut mycobiome to SARS-CoV-2 infection and disease progression need to be determined in future work (Zuo et al., 2020b).

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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