Review 1: "Gut Microbiota from Patients with COVID-19 Cause Alterations in Mice that Resemble Post-COVID Symptoms"

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**RR:C19 Evidence Scale** rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

**Review:**

This study aims to understand the functional role of gut microbiota in the long-term consequences of coronavirus disease-2019 (COVID-19). Compared with the healthy controls, post-COVID patients showed an increased abundance of multidrug-resistant *Enterobacteriaceae* in gut microbiota and reduced levels of short-chain fatty acids (SCFAs) in plasma. When the feces of post-COVID patients were transferred to germ-free mice, these animals showed increased susceptibility to lung infection and memory impairment. This method using germ-free mouse model of fecal microbiota transplantation (FMT) may partially reconstruct the microbiological and metabolic characteristics of gut microbiota of post-COVID patients in mice, which should be helpful to reveal the mechanisms by which gut microbes and gut microbial metabolites regulate the pathogenesis of COVID and post-COVID. Importantly, this study suggests that the gut microbiota derived from post-COVID patients may increase the susceptibility or severity of lung infection and memory impairment in mice. For example, mice transplanted with feces from post-COVID patients and infected with *Klebsiella pneumonia* induced more serious pathological damages in lung compartment. Thus, the aberrations of gut microbiota caused by COVID-19 infection may somehow contribute to long-term detrimental impact on health, even after the virus is eliminated. Interestingly, to explore the therapeutic potential of interventions targeting gut microbiota for post-COVID-19 symptoms, they used a mouse model infected with mouse hepatitis virus 3 (MHV-3), and it was implicated that probiotics supplementation might reverse the memory impairment.

This study showed that I-FABP, an index of intestinal epithelial injury, was increased upon FMT from post-COVID patients, but it may be useful to further carry out more immunohistochemical analyses to verify whether and how the gut microbiota of post-COVID patients indeed caused intestinal barrier damages. Also, although they found a range of important metabolites such as short-chain fatty acids (SCFAs) directly or indirectly produced by gut microbiota were significantly reduced in the plasma of post-COVID patients, they focused more on the roles of acetate in animal works. However, it may be helpful to further explore the abundance and functional changes of other SCFAs, and verify whether they played a protective or detrimental role involving in post-COVID symptoms. Furthermore, the infection model of MHV-3 virus was used to mimic COVID-19 infection, but the liver pathology and, particularly, hepatitis induced by MHV-3 virus infection...
might be significantly different from COVID-19 infection, which somehow conferred differences in disease phenotypes and mechanisms for memory impairment between MHV-3 and COVID-19 infections. Finally, it may be interesting to explore whether oral supplementations of *Bifidobacterium longum* can really help control the memory impairment of mice with FMT treatments from post-COVID patients.

Overall, this work not only provides additional pieces of critical evidence demonstrating that alternations of structure and functions of gut microbiota may be associated with pathogenesis of COVID-19, but also suggests that interventions targeting gut microbiota may be a potential treatment for sequelae after COVID-19. It should be interesting for further studies to explore the functional characteristics and underlying mechanisms of such diverse and complex interaction networks of virus-host, virus-other microbes (including gut microbiota), and gut microbiota-host in COVID-19 and potentially other infectious diseases.