Gut Dysbiosis Could Be a Major Factor for the Effects of Low-Grade Endotoxemia in COVID-19 Comment on: Low-Grade Endotoxemia and Thrombosis in COVID-19

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The intestinal microbiota plays a fundamental role in human health, particularly in immune system development and maintenance. Commensal bacteria and their metabolites not only promote immune responses but also provide anti-inflammatory mechanisms, establishing a strong but well-balanced immune system (1). Therefore, dysregulation of gut microbiota (gut dysbiosis) progresses inflammation and inflammation-associated diseases. Current evidence shows that gut dysbiosis is common in coronavirus disease 2019 (COVID-19) and is regarded as a major pathogenic factor of the disease (2). Gut dysbiosis can be caused by both SARS-CoV-2 infections and pre-existing chronic diseases, which are risk factors for severe COVID-19. Gut dysbiosis in COVID-19 is characterized by increased opportunistic bacteria such as those from the *Ruminococcus* species and decreased commensal bacteria such as *Faecalibacterium prausnitzii*, which is an important butyrogenic microbe in the large intestine. Butyrate is known to have anti-inflammatory effects through various mechanisms such as activation of regulatory T cells and inhibition of multiple signaling pathways (2). Therefore, gut dysbiosis not only causes proinflammatory effects but also reduces anti-inflammatory mechanisms.

Oliva et al. presented that the blood levels of lipopolysaccharides (LPS) were increased in patients with COVID-19 and correlated with increased gut permeability, indicated by higher zonulin levels (3). The increased levels of LPS contributed to the hyperinflammation and thrombosis, 2 characteristics of severe COVID-19. We posit that gut dysbiosis is one of the major causes for the detrimental effects of LPS endotoxemia in COVID-19; gut dysbiosis not only increases blood levels of LPS but also potentiates the effects of LPS.

Gut dysbiosis disrupts gut barrier functionality, which greatly contributes to LPS translocation into the intestinal mucosa and its accumulation in the systemic circulation. Commensal bacteria maintain gut barriers through multiple mechanisms including maintaining tight junction integrity, mucus production, and secretion of antimicrobial peptides to prevent the translocations of LPS and bacteria from the gut lumen into the mucosa and thence the circulation (4). In gut dysbiosis, the intestinal tight junction is disrupted, allowing the translocation of LPS and bacteria into the circulation and extra-intestinal organs. Many commensal bacterial metabolites are important in maintaining gut barrier integrity, and decreased metabolites in gut dysbiosis cause gut barrier disruption (4).

Anti-inflammatory effects of bacterial metabolites could be important for LPS-caused detrimental effects. An animal study reported that butyrate reduced the LPS/TLR4/NF-κB proinflammatory signaling pathway (5). Gut dysbiosis could also disturb bile acid metabolism, with decreased production of secondary bile acids and their derivatives. Secondary bile acids have a strong anti-pathobiont effect and thus are important for the homeostasis of gut microbes. Several derivatives of secondary bile acids, such as 3-oxolithocholic acid, isoallolithocholic acid, and isodeoxycholic acid, can activate regulatory T cells exerting anti-inflammatory effects (2). Tryptophan is decomposed by bacterial tryptophanase into indole, which has been demonstrated to have an anti-inflammatory effect. Reduced counteraction to LPS-induced detrimental effects by these commensal bacterial metabolites could allow low endotoxemia to progress to disease severity. Further understanding of gut dysbiosis in LPS-caused inflammation and thrombosis in COVID-19 could be valuable for the effective treatment of the disease.

CONFLICTS OF INTEREST

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REFERENCES

1. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157:121–41.
2. Chen J, Hall S, Vitetta L. Altered gut microbial metabolites could mediate the effects of risk factors in Covid-19. Rev Med Virol 2021;31: 1–13.
3. Oliva A, Cammisotto V, Cangemi R, et al. Low-grade endotoxemia and thrombosis in COVID-19. Clin Transl Gastroenterol 2021;12:e00348.
4. Ghosh S, Whitley CS, Haribabu B, et al. Regulation of intestinal barrier function by microbial metabolites. Cell Mol Gastroenterol Hepatol 2021;11(5):1463–82.
5. Luo QJ, Sun MX, Guo YW, et al. Sodium butyrate protects against lipopolysaccharide-induced liver injury partially via the GPR43/β-arrestin-2/NF-κB network. Gastroenterol Rep (Oxf) 2020;9:154–65.

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