Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Immunology 232 (2021) 108870

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Letter to the Editor

Commensal bacterial metabolites may strengthen the effect of anti-IL6 treatment for COVID-19

ARTICLE INFO

Keywords
Butyrate
Tocilizumab
COVID-19
Regulatory T cells

Hyperinflammation plays a central role in the pathogenesis of severe COVID-19 and thus anti-hyperinflammation is a key for the treatment of severe COVID-19 to reduce mortality [1]. The report by Corominas and colleagues demonstrated that the anti-IL6 receptor antibody tocilizumab (TCZ) importantly and significantly reduced the mortality rate of those patients diagnosed with moderate or severe COVID-19 compared with hospitalized patients' mortality rate [2]. Cytokines collaborate with other key features of COVID-19 such as direct viral infections and microvascular thrombosis to progress multi-organ failure [1]. Given that ACE2 is expressed in many cell types, SARS-CoV-2 may infect multiple organs. The grave vascular thrombosis may also block the blood supply to an organ, that as such then triggers severe consequences. In addition, the cytokine storm could be associated with lymphopenia, another characteristic of severe COVID-19, causing decreased clearance of the virus. A study reported that the combination of increased IL-6 levels and decreased $CD8^+$ T-cell frequency was a reliable predictor for COVID-19 caused mortality [3]. Although IL-6 is a major cytokine, many other proinflammatory cytokines are involved in hyperinflammation of severe COVID-19. Therefore, there is an opportunity to further inhibit hyperinflammation that reduces mortality with severe COVID-19. We posit that commensal bacterial metabolites could be an effective option to be combined with TCZ.

Many chronic diseases have been identified as risk factors such as lung disease, heart disease, hypertension, obesity, diabetes and kidney disease [1]. The effects expounded by these chronic diseases could be accounted for by widespread chronic and systemic inflammation. This could be mediated by gut dysbiosis. In all of these chronic diseases, the intestinal microbiota is dysregulated. In addition, SARS-CoV-2 can cause intestinal dysbiosis either through direct infection or the dysregulation of pro-inflammatory cytokines. Gut dysbiosis results in decreased commensal bacterial metabolites, that promotes chronic inflammation and decreased anti-inflammatory mechanisms. These commensal metabolites such as short-chain fatty acids, bile acid derivatives and tryptophan have anti-inflammatory and anti-pathobiont effects [1]. Butyrate, an anti-inflammatory short-chain fatty acid, has been extensively studied. In a healthy gut microbiota, butyrate is produced in millimolar levels [4]. It exerts anti-inflammatory effects through multiple mechanisms [1]. Butyrate can activate anti-inflammatory immune cells such as regulatory T cells and M2 macrophages. It also inhibits inflammatory signalling pathways through histone deacetylase-dependent and independent manners. Furthermore, butyrate has anti-viral and anti-bacterial effects. Butyrate can increase mucin secretion to decrease the contact of pathobionts with intestinal cells and enhance the production of defensins, which have direct effect on viruses [5]. In a rat gut epithelial organoid- model, a recent study demonstrated that butyrate could regulate genes essential for SARS-CoV-2 infection [6]. It also upregulated genes in TLR pathway to increase anti-viral ability of the host [6]. In addition, butyrate can increase the functionalities of gut barrier to prevent translocations of gut pathobionts and lipopolysaccharides into the circulation and thus reduce systemic inflammation.

There is a feed-forward effect in the formation of the cytokine storm in COVID-19. In the late stages, anti-inflammatory therapy may not be sufficient to overcome accumulated high levels of cytokines as well as already produced tissue damage and vascular thrombosis. Other studies have also shown that TCZ was effective in the early stages of infection when no mechanical respiratory support was required [7]; but not effective when enrolled patients needed mechanical ventilation [8]. An early application of anti-inflammatory therapy which could combine anti-IL-6 therapy and commensal bacterial metabolites such as butyrate could greatly reduce the mortality rate of COVID-19.

We declare that we have no conflicts of interest and no external funds.

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Received 3 February 2021; Accepted 28 September 2021
Available online 30 September 2021

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