COVID-19 and Coagulopathy

To the Editor:

We read with interest the recent review article by Rodriguez and colleagues regarding endothelial dysfunction and consequent thrombotic complication in patients with coronavirus disease (COVID-19) (1). Here, we would like to add a point. We will provide supplementary explanation on a molecular group (e.g., IL-1, IL-6, and TNF-α) that has been implicated in coagulation activation in the paper.

We wish to explain the complex role of IL-6 in coagulopathy accompanied by severe inflammation. Using IL-6 knockout (IL-6−/−) mice, we have previously demonstrated that IL-6 serves as a protector in coagulatory disturbance and thrombocytopenia during devastating systemic inflammation induced by intraperitoneal administration of bacterial endotoxins (LPS) (2), which was evidenced by prothrombin time and activated partial thromboplastin time. Furthermore, we have confirmed that in the presence of LPS, α2-plasmin inhibitor activity was significantly lower in IL-6−/− mice than in wild-type mice, indicating that IL-6 can partially inhibit LPS-provocated fibrinolysis by enhancing α2-plasmin inhibitor activity (3). Interestingly, fibrin degradation product was significantly lower in the IL-6−/− mice administered with LPS than in the wild-type mice, whereas D-dimer was comparable in both groups (unpublished observation; these complicated results require future research for further clarification). Regardless, IL-6 may not be introduced in the same way as other proinflammatory cytokines, such as IL-1 and TNF-α, in coagulatory disturbance with persistent inflammation.

From the Authors:

We read the letter from Dr. Inoue and colleagues with interest and recognize the importance of pointing out that IL-6...
contribution to coronavirus disease (COVID-19)–related inflammation and thrombosis may be different from other inflammatory cytokines. Hence, we thank Dr. Inoue and colleagues for their interest in our recently published review and for sharing some interesting results that would be beneficial in COVID-19 research (1).

IL-6 is a commonly known proinflammatory cytokine induced under acute distress with a relevant role in the inflammatory profile of many different diseases (2). However, it has been recognized for some time that IL-6 could also display antiinflammatory functions inhibiting TNF-α and IL-1, thus playing an important role in controlling the level of proinflammatory cytokines (3). As Dr. Inoue and colleagues point out, the role of IL-6 as a potential guard against coagulation unbalance needs to be further validated. Although some are in favor that the elimination of IL-6 attenuates coagulation and thrombus formation (4), some recent animal studies have shown that the administration of IL-6 antibody delays thrombus resolution (5). Further studies are needed, particularly one that would assess the efficacy of IL-6 inhibitors as a treatment strategy in the current COVID-19 pandemic.

On the other hand, it is generally accepted that the identification of useful biomarkers to detect and control a proinflammatory response to COVID-19 infection in the early stages of viral infection is crucial. There are several articles suggesting the fact that elevated IL-6 levels may be present in major proportion in patients with severe COVID-19 (6) and that the levels of IL-6 should be monitored in all patients with COVID-19.

In this regard, recent evidence indicates that systemic IL-6 levels in patients with COVID-19, owing to its central role in activating and maintaining the inflammatory response, can be considered an important biomarker for predicting severity of the disease, poor prognosis, and the need for intensive care (7). Although monitoring IL-6 levels in COVID-19 infection could be readily applied in the clinical practice, future research aiming to identify other biomarkers with poor clinical evolution to mitigate processes such as hyperinflammation and to understand the mechanisms underlying functional immune impairment are required to significantly improve patient survival.

Finally, we would like to remark that our review “Pulmonary Endothelial Dysfunction and Thrombotic Complications in Patients with COVID-19” is mainly focused on endothelial dysfunction and thrombotic complications in patients with COVID-19. As shown in Table 1 of our manuscript, we also focus on other relevant parameters related to COVID-19 development and severity, such as lower concentration of platelets and elevated CRP and D-dimer levels, among others, as predictive markers for adverse COVID-19 evolution.

We would like to thank Dr. Inoue and colleagues for their interesting and intriguing results, and we would like to encourage them to further investigate the role of IL-6 in thrombus formation and resolution in patients with COVID-19.

**References**

1. Rodriguez C, Luque N, Blanco I, Sebastian L, Barbera JA, Peinado VI, et al. Pulmonary endothelial dysfunction and thrombotic complications in patients with COVID-19. *Am J Respir Cell Mol Biol* 2021;64:407–415.

2. Taheri MY, Davies DM, Maher J. The role of the interleukin (IL)-6/IL-6 receptor axis in cancer. *Biochem Soc Trans* 2018;46:1449–1462.

3. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, et al. IL-6 is an anti-inflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J Clin Invest* 1998;101:311–320.

4. Senchenkova EY, Komoto S, Russell J, Almeida-Paula LD, Yan LS, Zhang S, et al. Interleukin-6 mediates the platelet abnormalities and thrombogenesis associated with experimental colitis. *Am J Pathol* 2013;183:173–181.

5. Nosaka M, Ishida Y, Kimura A, Kuninaka Y, Tanaya A, Ozaki M, et al. Crucial involvement of IL-6 in thrombus resolution in mice via macrophage recruitment and the induction of proteolytic enzymes. *Front Immunol* 2020;10:3150.

**Author disclosures**

*Corresponding author (e-mail: olgaturac@gmail.com). Correspondence*
6. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP) [preprint]. medRxiv; 2020 [accessed 2020 Feb 12]. Available from: https://www.medrxiv.org/content/10.1101/2020.02.10.20021832v1.

7. Gubernatorova EO, Gorshkova EA, Polinova AI, Drutskaya MS. IL-6: relevance for immunopathology of SARS-CoV-2. Cytokine Growth Factor Rev 2020;53:13–24.

Erratum: Sirtuin 1 Promotes Hyperoxide-Induced Lung Epithelial Cell Death Independent of NF-E2–Related Factor 2 Activation

The authors of an article published in 2016 (1) were notified of an anomaly in the figures. In the published article the phase contrast images of room air–exposed SIRT1-siRNA– and NRF2-siRNA–transfected cells in Figure 3C and Figure 4C contain an area of duplication. The authors were unable to locate the original figures, but have now provided a corrected version of Figure 3C and Figure 4C after repeating the experiments. The authors state that this correction does not change the scientific interpretation or conclusions reached in the article, and they apologize for this error.

Reference

1. Potteti HR, Rajasekaran S, Rajamohan SB, Tamatam CR, Reddy NM, Reddy SP. Sirtuin 1 promotes hyperoxia-induced lung epithelial cell death independent of NF-E2–related factor 2 activation. Am J Respir Cell Mol Biol 2016;54:697–706.

Copyright © 2021 by the American Thoracic Society