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.

International Journal of Infectious Diseases 107 (2021) 232–233

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Perspective

Potential value of circulating endothelial cells for the diagnosis and treatment of COVID-19

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ARTICLE INFO

Article history:
Received 21 January 2021
Received in revised form 29 April 2021
Accepted 1 May 2021

Keywords:
SARS-CoV-2
COVID-19
Endothelial cell
Diagnosis
Treatment

ABSTRACT

The ongoing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has been a formidable global challenge. As yet, there are very few drugs to treat this infection and no vaccine is currently available. It has gradually become apparant that coronavirus disease 2019 (COVID-19) is not a simple disease involving a single organ; rather, many vital organs and systems are affected. The endothelium is one target of SARS-CoV-2. Damaged endothelial cells, which break away from organs and enter the bloodstream to form circulating endothelial cells, were recently reported as putative biomarkers for COVID-19. Modulation of the expression level of sphingosine-1 phosphate via sphingosine kinase activation can control endothelial cell proliferation and apoptosis. As such, it may be possible to obtain a sensitive and specific diagnosis of the severity of COVID-19 by assessing the absolute number and the viable/apoptotic ratio of circulating endothelial cells. Furthermore, a focus on the endothelium could help to develop a strategy for COVID-19 treatment from the perspective of endothelial protection and repair.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread throughout the world. To date, there have been more than 33 million confirmed cases of coronavirus disease 2019 (COVID-19) and more than one million deaths. At the onset of the pandemic, COVID-19 was considered to be a mono-organ disease involving lesions; however, the pulmonary system, gastrointestinal system, kidney, heart and liver have now been identified as targets of SARS-CoV-2 infection (Cheung et al., 2020; Puelles et al., 2020). The endothelium has also been implicated (Varga et al., 2020). A recent study (Guervilly et al., 2020) identified a possible correlation between increased levels of circulating endothelial cells (CECs), which are the deciduous endothelial cells from the injured organs or tissues circulating in blood, and the severity of COVID-19. The CEC levels in patients with COVID-19 who required intensive care unit (ICU) treatment were significantly higher compared with patients who did not need ICU treatment. Additionally, the study found a strong relationship between disease severity and the extent of endothelial injury; as such, the CEC level was postulated as a putative biomarker for the severity of COVID-19. Another study reported that the viable/apoptotic CEC ratio was significantly different in patients with COVID-19, although the absolute number of CECs was not significantly different compared with healthy controls (Mancuso et al., 2020). Furthermore, a fraction of CECs are associated with endothelial progenitor cells, which can be infected by SARS-CoV-2. However, as stem cells do not express specific receptors or limited areas of the cell membrane are covered with target receptors, these features limit direct contact and cross-talk between the virus and stem cells (Bagheri et al., 2021). This contradiction means that there is a need to consider the potential infectious mechanism cautiously, especially in the clinical transplant setting from patients with COVID-19.

The endothelium is one of the largest organs in the body; its primary function as a barrier depends on its homeostasis. A recent study demonstrated that patients with COVID-19 have a higher risk of severe outcomes when they have hypertension or diabetes, which can cause endothelial damage (Levi et al., 2020). Endothelial cells in children typically have a more complete structure and they function better compared with those in adults; consequently, endothelial tissue in children is more resistant to viral attack (Hepponstall et al., 2017). Adverse effects of COVID-19, such as hypercoagulation and vascular damage, rarely occur in children with the disease (Ludvigsson, 2020). On the contrary, researchers (Rauch et al., 2020) provided the results of a functional assay demonstrating a direct effect of dysregulation of immune response

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https://doi.org/10.1016/j.ijid.2021.05.001

on endothelial damage in patients with COVID-19, and declared that the endothelial damage is associated with immunopathology and may occur in parallel with intracellular SARS-CoV-2 infection. This is direct evidence with diagnostic value of endothelial damage correlated with COVID-19.

The above findings imply that the absolute number of CECs is closely related to the severity of COVID-19, and the viable/apoptotic CEC ratio differs significantly between patients with COVID-19 and healthy controls. To some extent, CECs should be considered as a potential biomarker for COVID-19, based on their number and classification.

Many registered clinical trials for COVID-19 have been conducted, such as for antiviral and antimalarial treatment (Lythgoe and Middleton, 2020), but very few have found a reduction in overall mortality or viral load (Cao et al., 2020). Cystic fibrosis transmembrane conductance regulator (CFTR) has been found to maintain the stability of lung endothelium (Tsai and Han, 2016). CFTR dysfunction can increase the permeability of endothelial cells and may aggravate lung inflammation. Sphingosine-1 phosphate (S1P) is a sphingosine derivative which has five subtypes (S1P1–S1P5) with diverse expression levels modulated by sphingosine kinase (SphK, including SphK1 and SphK2). S1P regulates various biofunctions, including stimulation of cell proliferation by SphK1 and promotion of apoptosis of injured cells by SphK2 (Tsai and Han, 2016), and has been proven to ameliorate the negative effect of CFTR dysfuction. By modulating the expression level of S1P via the activation of SphK, the proliferation (stimulated by SphK1) and apoptosis (promoted by SphK2) of endothelial cells can be controlled (Mohammed and Harikumar, 2017). Endothelial homeostasis is maintained through these two pathways, making it more resistant to viral and bacterial invasion. Hence, physicians should aim to maintain endothelial function and ameliorate endothelial damage in patients to prevent SARS-CoV-2 infection and reduce the severity of COVID-19, particularly until there is a material breakthrough in SARS-CoV-2 vaccine and drug development.

A focus on the endothelium and endothelial cells provides the opportunity to obtain a sensitive and specific diagnosis of the severity of COVID-19 by assessing the absolute number and the viable/apoptotic ratio of CECs. Furthermore, this focus could aid in a COVID-19 treatment strategy from the perspective of endothelial protection and repair.

Author contributions

JSY conceptualized the study. XCZ collected and analysed the data. JSY, MJ and XCZ interpreted the results. JSY and XCZ drafted the manuscript. JSY finalized the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

None declared.

Funding

This work was supported by the Special Fund for Economic and Scientific Development in Longgang District, Shenzhen City, Guangdong Province (No. LGKCYLWS2020043).

Ethical approval

Not required.

Acknowledgements

The authors wish to thank Dr Xigang Jing, a senior researcher at the Medical College of Wisconsin, Milwaukee, WI, USA, who provided academic support regarding endothelial physiology.

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