International Journal of Infectious Diseases 110 (2021) 330–331

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

LETTER TO THE EDITOR

Influenza immunization and COVID-19—can viral structure be responsible for the effect?

We would like to express our gratitude for the readers' interest in our published article entitled "Pneumonia in medical professionals during COVID-19 outbreak in cardiovascular hospital" published in the *International Journal of Infectious Diseases* (Ilic et al., 2021).

In the study it was found that medical professionals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who had been immunized against seasonal influenza had a lower incidence of computed tomography-confirmed bilateral pneumonia. We sought to explain this by presenting evidence of structural similarities between the *Coronaviridae* (SARS-CoV-2) and *Orthomyxoviridae* (influenza virus) families in the structural glycoprotein named haemagglutinin esterase (HE), which was shared by lateral gene transfer around 8000 years ago. These similarities could lead to cross-reactivity and enhanced immunity against SARS-CoV-2 in persons who have previously received the seasonal influenza vaccine (Ilic et al., 2021).

Zandi and colleagues have questioned this by stating that SARS-CoV-2 does not have a distinctive HE glycoprotein and thus cross-reactivity could not be the reason for the enhanced immunity against SARS-CoV-2 in persons vaccinated against influenza. However, this statement is only partially true.

SARS-CoV-2, like other *Coronaviridae*, has a similar structure consisting of spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein. Although not identified as a distinct protein in SARS-CoV-2, HE has been identified previously in the *Betacoronavirus* family as a part of the S1 domain that helps viral attachment to the surface of the host cell using sialic acid on the host cell's glycoproteins, while HE within the S1 domain exhibits sialate O-acetylesterase receptor destroying activity (Huang et al., 2015). Evolutionary adaptation to the sialoglycome of the human respiratory tract has led to a loss of HE receptor-binding activity and a reduction in virion-associated esterase activity (Bakkers et al., 2017). However, the S glycoprotein of SARS-CoV-2 has retained properties regarding host receptor binding that are common for *Coronaviridae* and influenza virus group C and D, indicating conserved recognizing structures. Comparative protein sequence analysis showed that the short region of the novel coronavirus S2 subunit that undergoes conformational changes to attach to host cells resembles the structure of influenza H3N2 haemagglutinin. Although the S protein of the novel coronavirus differs from the binding proteins of influenza virus, there is evidence that antiviral drugs that were used to treat influenza have activity against SARS-CoV-2. A small study explored the potential effects of umifenovir, a drug registered for influenza treatment, on SARS-CoV-2, by comparing structural similarities between SARS-CoV-2 and influenza H3N2 trimerization domains involved in drug binding. When superimposed, the binding regions for the drug of both viral species demonstrated significant structural similarities (Vankadari and Wilce, 2020; Vankadari, 2020a).

Although evidence regarding the structure and function of the novel coronavirus is emerging, it must be noted that immunization itself is a process that stimulates the immune system of the vaccinated person, so that the response to another pathogen may be enhanced leading to the observed associations found in our study.

Since COVID-19 is a multifaceted disease, the real impact of influenza immunization on the incidence and severity of the disease can only be explored in a large-scale retrospective study where other factors that have a proven influence on the severity of the disease, like diabetes, hypertension, and obesity, are well balanced between the study groups.

Declarations

Funding source: This research project was not sponsored or partially funded by any agency or company.

Ethical approval: The manuscript has been approved by the Institutional Ethics Committee.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Bakkers MJ, Lang Y, Feitsma LJ, Hulswit RJ, de Poot SA, et al. Betacoronavirus Adaptation to Humans Involved Progressive Loss of Hemagglutinin-Esterase Lectin Activity. Cell Host Microbe 2017;21(3):356–66. doi:10.1016/j.chom.2017.02.008.

Huang X, Dong W, Milewska A, Golda A, Qi Y, et al. Human Coronavirus HKU1 Spike Protein Uses O-Acetylated Sialic Acid as an Attachment Receptor Determinant and Employs Hemagglutinin-Esterase Protein as a Receptor-Destroying Enzyme. J Virol 2015;89(14):7202–13. doi:10.1128/JVI.00854-15.

Ilic I, Zdravkovic M, Timcic S, Stojanovic DU, Bojic M, Loncar G. Pneumonia in medical professionals during COVID-19 outbreak in cardiovascular hospital. Int J Infect Dis 2021;103:188–93. doi:10.1016/j.ijid.2020.11.156.

Vankadari N. Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. Int J Antimicrob Agents 2020;56(2). doi:10.1016/j.ijantimicag.2020.105998.

Vankadari N, Wilce JA. Emerging Wuhan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microb Infect 2020;9:601–4. doi:10.1080/22221751.2020.1739565.

Ivan Ilic*
Department of Cardiology, Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia
Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Dragana Unic Stojanovic
Faculty of Medicine, University of Belgrade, Belgrade, Serbia
Department of Anaesthesia and Intensive Care Medicine, Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia

https://doi.org/10.1016/j.ijid.2021.07.055

Goran Loncar
Department of Cardiology, Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia
Faculty of Medicine, University of Belgrade, Belgrade, Serbia

*Corresponding author: Ivan Ilic, Department of interventional cardiology, Institute for cardiovascular diseases Dedinje, Heroja Milana Tepica 1, 11040 Belgrade, Serbia. Tel/Fax: +381-11-3601700.
E-mail address: ivan1ilic@yahoo.com (I. Ilic)