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.

Medical Hypotheses 144 (2020) 110020

Contents lists available at ScienceDirect

Medical Hypotheses

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

Pulmonary surfactant itself must be a strong defender against SARS-CoV-2

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ARTICLE INFO

Keywords:
SARS-CoV-2
Pulmonary surfactant
ACE2
Alveolar epithelial type II cell

ABSTRACT

Pulmonary surfactant is considered to be one of the soaps. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the other enveloped viruses become very weak against surfactant. The SARS virus binds to angiotensin-converting enzyme (ACE2) receptor and causes pneumonia. In the lung, the ACE2 receptor sits on the top of lung cells known as alveolar epithelial type II (AE2) cells. These cells play an important role in producing surfactant. Pulmonary surfactant is believed to regulate the alveolar surface tension in mammalian lungs. To our knowledge, AE2 cells are believed to act as immunoregulatory cells; however, pulmonary surfactant itself has not been believed to act as a defender against the enveloped viruses. This study hypothesises that pulmonary surfactant may be a strong defender of enveloped viruses. Therefore, old coronaviruses merely cause pneumonia. On the contrary, new SARS-CoV-2 can suppress the production of surfactant that binds to the ACE2 of AE2 cells. The coronavirus can survive in the lung tissue because of the exhaustion of pulmonary surfactant.

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a worldwide pandemic, which has greatly affected humanity.

The crystal structure of the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 is bound to the cell receptor angiotensin-converting enzyme (ACE2) [1]. In the lung, the ACE2 receptor is located on the top of lung cells known as alveolar epithelial type II (AE2) cells. However, the reason for the binding of virus to the ACE2 receptor is not known yet.

The AE2 cells are known to synthesize and secrete the pulmonary surfactant that regulates the alveolar surface tension in mammalian lungs [2]. AE2 cells proliferate, differentiate into alveolar epithelial type I cells, and remove the apoptotic AE2 cells by phagocytosis, thus contributing to the repair of epithelial cells. Moreover, the AE2 cells may act as immunoregulatory cells [2]. Surfactant is considered to modulate immune responses [3]. Surfactant components are synthesized primarily by the alveolar type II cell [3]. Surfactant contains four associated proteins, surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Two of these proteins, SP-A and SP-D, are hydrophilic, and the others are hydrophobic [3]. Pulmonary collectins (SP-A and SP-D) bind to viruses to facilitate pathogen removal. SP-A and SP-D prevent infection of epithelial cells through viral neutralization, agglutination, and enhanced phagocytosis [3]. The most well-described function of the collectins is their ability to opsonize pathogens and facilitate their phagocytosis by cells of the innate immune system, such as macrophages and monocytes, as well as regulate the production of cell-derived mediators [3]. SP-A and/or SP-D bind to hemagglutinin and neuraminidase of influenza A virus to inhibit their activity. Pulmonary collectins also bind to glycoproteins of viruses, including HIV, RSV, and SARS coronavirus [3]. In addition to pulmonary collectins, the surfactant lipid components also inhibit RSV infection [3].

Pulmonary surfactant is considered to opsonize pathogens and facilitate their phagocytosis by cells of the innate immune system [3]. To our knowledge, pulmonary surfactant itself has not been believed to act as a strong defender against the enveloped viruses.

Coronavirus is one of the enveloped viruses, which are very weak against surfactant.

Soap is a surface-active agent (surfactant). As the soap molecule penetrates into the virus coat, it splits it apart, further breaking the virus open and releasing its contents into the surrounding soapy water [4].

The hypothesis

This study hypothesises that pulmonary surfactant itself not only reduces surface tension and increases lung compliance, but also may be a strong defender against the enveloped viruses. Therefore, the new coronavirus may suppress the pulmonary surfactant production of AE2 cells to survive by using the ACE2 receptor in the infected lung tissues.

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https://doi.org/10.1016/j.mehy.2020.110020
Received 30 April 2020; Received in revised form 16 June 2020; Accepted 18 June 2020
Available online 20 June 2020

Evaluation of the hypothesis

Old coronaviruses are known to be common cold viruses and merely cause pneumonia. Some of the evolved enveloped viruses including SARS-CoV-2 can survive in the lung probably by suppressing the production of pulmonary surfactant. This surfactant exhaustion probably affects some of the symptoms such as lung atelectasis and acute respiratory distress syndrome. The main pathologic findings from the cases of COVID-19 pneumonia include diffuse alveolar type II cell hyperplasia [5]. This may be a reactive change to surfactant exhaustion.

The inhalation of surfactant or surfactant production stimulant will reduce alveolar surface tension and increase lung compliance and may kill the new coronavirus.

Ciclesonide, which was reported as one of the clinically effective drugs against COVID-19, may contain surfactant such as oleic acid [6]. Oleic acid itself may be effective for the management of COVID-19.

Ambroxol and Bromhexine stimulate the synthesis and release of pulmonary surfactant by the AE2 cells. Therefore, they may be not only used for the treatment but also for the prophylactic administration. Chronic obstructive pulmonary disease and asthma appear to be underrepresented in the comorbidities reported for patients with coronavirus disease (COVID-19). A similar pattern was observed with SARS [7]. This study's hypothesis can resolve this paradox. Ambroxol and Bromhexine are commonly prescribed for both diseases.

On the other hand, bromhexine inhibits TMPRSS2. Inhibits TMPRSS2-specific viral entry is considered to be effective against SARS-CoV-2 [8]. Based on this theory, a clinical trial (registration number NCT04273763), carried out by WEPON Pharmaceutical Group Co. Ltd., is the first human body-based preliminary exploratory randomized-controlled clinical study on treating COVID-19 with bromhexine hydrochloride tablets (BHT) [8]. The study results showed the signs of efficacy from multiple angles using BHT. Treatment with BHT alleviated lung injury to a certain extent, and no severe adverse effects were experienced [8]. This theory is different from my hypothesis, however, clinically bromhexine was proved to be effective against COVID-19.

Ambroxol does not inhibit TMPRSS2. However, Ambroxol was found as an ACE2 binding agent according to an artificial intelligence (AI) drug target screening done by researchers at the School of Basic Medicine Sciences at Peking University [9]. According to the "Handbook of COVID-19 Prevention and Treatment", produced by the First Affiliated Hospital, Zhejiang University School of Medicine, they are already using Ambroxol in the treatment of moderate and severe COVID-19 patients [10]. From their clinical experience, they have concluded that Ambroxol is effective against COVID-19. My hypothesis can explain the efficacy of both drugs.

Vitamin D supplementation could reduce the risk of influenza and COVID-19 infections and deaths [11]. This may also explained by pulmonary surfactant as vitamin D increases the synthesis of surfactant [12].

Consequences of the hypothesis

Pulmonary surfactants, some chemical surfactants and surfactant production stimulants may be effective not only for the treatment but also for the prophylactic administration for COVID-19 and the other enveloped virus pneumonia.

Declaration of Competing 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.

Acknowledgements

The author would like to thank Enago (www.enago.jp) for the English language review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110020.

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