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 143 (2020) 110066

Contents lists available at ScienceDirect

Medical Hypotheses

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

A hypothesis on the role of the human immune system in covid-19

A B S T R A C T

The COVID-19 pandemic has not spared any continent. The disease has affected more than 7,500,000 individuals globally and killed approximately 450,000 individuals. The disease is caused by a very small virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an enveloped single-stranded RNA virus with a spike-like structure on its envelope that can interact with the angiotensin-converting enzyme 2 (ACE2) receptor after cleavage. ACE2 receptors are present in the human lungs and other organs. SARS-CoV-2 is a new virus that belongs to the subgenus Sarbecovirus; viruses in this subgenus have spread widely in the previous years and caused outbreaks of severe acute respiratory syndromes.

This hypothesis provides insights into a possible human immune response to SARS-CoV-2. It is concise in the immune system that stimulates respiratory mucosa sensitivity, which increases mucus secretion and decreases clarity. Sex determining region Y box 2 (SOX2) is required to regulate epithelial cell proliferation by increasing the number of goblet cells and decreasing the number of other types of cells. SOX2 may be involved in the pathogenic process of anosmia, which is the loss of the sense of smell, and ageusia, which is the loss of taste functions of the tongue; both are symptoms of COVID-19. The most serious point in this cascade is mucus hypersecretion, which can be an underlying cause of hypoxia and therefore, a cause of acute respiratory distress syndrome in infected patients. Mucus hypersecretion leads to mucus plug formation. Additionally, airway, alveoli, and endotracheal tube blockages can occur and be complicated by emphysema and hypoxia, which are resistant to oxygenation. These symptoms may be more severe if a patient is especially sensitive to coronavirus. This letter provides suggestions for drugs that might be useful in the treatment of COVID-19; however, further analysis is needed.

Respiratory tissue hypersensitivity

SARS-CoV-2 RNA was detected with a higher load in nasal swabs than in throat swabs in both symptomatic and asymptomatic patients [1]. Sungnank et al. [2] believe that the nasal epithelium is an initial target of infection and serves as a reservoir of SARS-CoV-2 for transmission and spread to the lower respiratory tract. Pneumatization is the process of development of air-filled sinuses in the skull bone [3], and paranasal sinus pneumatization is usually seen at birth; for the maxillary sinuses, pneumatization may occur at 9 months of age to ethmoid and sphenoid sinuses. After the age of 5 years, pneumatization may be seen in the frontal sinuses [4]. Sinuses are part of the upper respiratory system; however, there is currently no information regarding the effect of COVID-19 on them; imaging by a paranasal CT scan may clarify this point and explain the initiation of infection and delayed negative PCR results, especially in children with a mild clinical presentation of the disease.

The respiratory mucosa is an organ that acts as a defensive mechanism after exposure to foreign bodies, such as viruses. It traps the virus via sticky secretions and then moves it out via the cilia [5]. Transmission of SARS-CoV-2 is associated with air droplets; mucus traps virus particles inside the body and outside of the body. Arumugham suggests that the novel coronavirus hyperstimulates the mucosa through a type I hypersensitivity reaction that is similar to the pathophysiology of dengue virus and some other viruses, which trigger an elevation in inflammatory biomarkers as an immune response [6]. This is supported by other studies showing that both SARS-CoV-1 and SARS-CoV-2 excessively stimulate the human inflammatory response; therefore, disease severity cannot be predicted by the viral load [7–9]. Chronic obstructive pulmonary disease (COPD) is an inflammatory disease associated with a high risk of pneumonia-related mortality and a lower immune response. This disease causes a persistent increase in mucus production; some treatments such as inhaled steroids may mitigate this risk [10]. If SARS-CoV-2 infects COPD patients, it will increase the severity of the infection by up to five-fold compared to infection in normal individuals [11]. Indeed, COVID-19 pathological investigations showed that the inflammatory reaction manifested as hypersensitivity pneumonitis rather than viral pneumonitis, as shown in a study conducted by Sufang Tian et al. [12]. This pathological information encouraged clinicians to add a steroid as an anti-inflammatory drug for the treatment regime of COVID-19 [12,13]. These pathological findings consider SARS-CoV-2 as an allergic antigen for respiratory mucosa; it stimulates mucus secretion and alters its chemical structure to enhance the entry of the virus into cells.

Mucus hypersecretion induced by antigens or allergens is a characteristic response of many respiratory diseases, including cystic fibrosis, bronchitis, and asthma. In all of these diseases, secretory cells are enhanced by different mechanisms, such as hyperplasia, metaplasia, or changes in the chemical structure of the mucus. The mucus secreted is composed of water and mucin, which has the properties of both a deformable solid and a gooey fluid. Mucins are enormous glycoproteins that are rich in threonine and serine residues. They are covalently associated with sugar chains that are anionic because of carboxyl or sulfate bundles. Several genes such as MUC5AC and MUC5B are known to encode mucins that are cysteine-rich, which allow the establishment of disulfide bonds that contribute to the polymers being produced in the airways. This arrangement and the profundity of the periciliary layer appear to play a pivotal role in the control of transport via mucociliary clearance within the airway routes. [14,15]. Mucus gel can build a macromolecule, which is a polymer of a complex network removable by S:S bond cleavage [5]. Recently, others have examined the role of

https://doi.org/10.1016/j.mehy.2020.110066
Received 18 June 2020; Accepted 29 June 2020

accumulation of mucus and mucin secretion in the progression of obstructive lung disease. Lack of MUC5B contributes to mucus aggregation in the nasal airways [16].

The mechanism underlying the regulation of mucogenesis is still not clear; however, many studies have focused on this aspect. This paper reviews the mechanism most compatible with the COVID-19-related clinical presentation. SOX2 is a member of the *sex* determining *region Y box* gene family that encodes transcription factors. SOX2 belongs to the SOX B1 subgroup, which contains both SOX1 and SOX3 [17]. SOX2 is essential for the morphogenesis of the normal trachea and lungs and is exclusively expressed in the epithelium of the trachea and airways [18].

Tompkins et. al. concluded that allergen-induced goblet cell differentiation and mucus production were absent in the respiratory epithelium without SOX2. They found that SOX2 is required to activate the proliferative process of the goblet, ciliated, and Clara cells to extend mucus production following exposure to allergens. [19,20].

In patients with COVID-19, symptoms of olfactory and gustatory dysfunction were observed in 85.6% and 88% of patients, respectively [21]. A study by Packard and his colleagues revealed that retroviral infection can affect SOX2 in mice, which might disturb the production of the olfactory epithelium [22]. Studies on humans have revealed that SOX2 in the olfactory epithelium plays a role in suppressing neuronal differentiation [23]. After data analysis of ACE 2 receptor expression, Brann et al. suggested that SARS-CoV-2 suppresses olfactory function by affecting olfactory supporting cells, perivascular, and stem cells, while not affecting neurons [24].

COVID-19 pneumonia presents an atypical form of atypical respiratory distress syndrome because, in COVID-19, there is a dissociation between the severity of hypoxemia and relatively high compliance of alveoli to ventilator pressure; additionally, lung mechanics indicate that there is a well-preserved lung gas volume in affected patients [25].

According to Rancé et al. [26], sensitivity to allergens is more frequent among children older than 6 years; sensitivity increases over time as dermatological changes affect respiratory symptoms and result in more severe anaphylaxis in older children [27]. Reviewing these hypersensitivity theories is suggested as the cause of mild symptoms of COVID-19 in children.

Suggested treatments based on the hypothesis

Bromhexine hydrochloride is a mucolytic agent that causes only a few mild side effects. It may serve as either a new therapeutic agent during the early stages of COVID-19 or as a preventive agent by blocking the entry of SARS-CoV-2 into alveolar cells via the TMPRSS2 receptor. Therefore, it can be used as an antiviral agent [28]. It plays a role in the proteolytic activation and invasion of the human airway epithelium by the influenza virus [29] as well as SARS and MERS coronaviruses [30]. N-acetylcysteine was also used for the prevention and treatment of COVID-19, but only in limited clinical trials [31]. In addition, this paper suggests that mucolytics may play a role in the treatment of SARS-CoV-2 infection by decreasing the viscosity of mucus, which allows the virus to be washed out of the body as quickly as possible.

Steroids are effective in controlling allergic respiratory diseases such as asthma; in contrast, nonsteroidal anti-inflammatory (NSAID) drugs may exacerbate asthma symptoms because their mechanism involves increasing leukotrienes.

A retrospective study showed that low doses of a steroidal anti-inflammatory drug early in the disease process were useful against COVID-19 and were associated with faster improvement of pneumonia [32]. Some clinical observational data revealed that symptoms of COVID-19 were exacerbated after the addition of an NSAID to the therapy; therefore, it was advised to avoid its usage [33]. If effective, the use of mucolytics and steroids in the treatment of SARS-CoV-2 infection may support our hypothesis of mucosal hypersensitivity.

Conclusion

SARS-CoV-2 is a small virus that is not able to cause all the COVID-19 symptoms. The response of the human body and its malfunction are responsible for the main pathogenesis of COVID-19. The immune system of the host may treat SARS-CoV-2 as an allergen and stimulate allergic immunity as a defensive mechanism. This paper suggests that mucosal hypersensitivity plays a role in COVID-19. SARS-CoV-2 may induce SOX2 to increase goblet cell proliferation, increase mucus hypersecretion, and decrease Clara and specialized epithelial cells, as seen in other allergic and inflammatory diseases. This analysis explains the differences in the severity of disease presentation. This review suggests drugs that might be useful in the treatment of COVID-19, but further investigation is required.

Funding source

This study did not receive any grant or funding from any department or institute.

Acknowledgement

None.

Conflict of interest statement

The authors declare they have no conflict of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110066.

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