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COVID-19

Lung Barrier Function in COVID-19?

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Abstract
The novel coronavirus COVID-19 appears to strike some people more intensely than others. Some people only experience mild symptoms while others require hospitalization and ventilation. With the virus becoming more prevalent day by day, it is not just the elderly, but even young people are falling seriously ill. Various researchers across the world state that specific cells in the nasal passages, intestines, and lungs may be more susceptible to the infection. Shifting the focus and research towards epithelium might provide new insight towards understanding COVID-19. This article is an overview of how epithelium permeability in COVID-19 may associate with comorbidities and other factors.

Keywords COVID - 19 · Epithelial barrier · Lung function · Mortality rate · Immune response · Inflammatory actions · Comorbidities · Epithelial permeability

Epithelium and Immunity

For decades, epithelial cells in innate immunity have been known to prevent the growth of bacterial and other microorganisms in the mucosal membrane [1]. Gong et al. [2] in his study shows that besides its mucociliary clearance feature, epithelial cells are now known to kill or neutralize microorganisms by producing many molecular families. Epithelial cells play a significant role in immune response regulation, inflammation, and host response. Although the role varies depending upon the pathogens and antigens, most of the diseases have a common pathology that includes marked epithelial cell activation in the upper airways or lower airways or both. Accumulating evidence by Schleimer et al. [3] suggests that epithelial cells are essential in initiating, regulating and maintaining the airway's innate and adaptive immune response.

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Pathogenesis of SARS-CoV-2

The inhaled SARS-CoV-2 virus likely begins the replication on attachment to the epithelial cells in the nasal cavity. Angiotensin-converting enzyme 2 (ACE2) is the primary receptor for SARS-CoV2 and SARS-CoV. The virus spreads locally but has a minimal innate immune response. At this point, nasal swabs will detect the virus [4, 5]. These individuals are infectious although the viral burden may be low. Clinically manifested at this time is the COVID-19 disease. Viral epithelial infected cells are an important source of beta and lambda interferons [6]. Determining the innate immune response of the host may improve predictions of the disease's subsequent course, and may require more aggressive monitoring. The disease would be mild for about 80% of the infected patients and mainly confined to the upper and conductive airways. Unfortunately, about 20% of the patients infected will advance to stage 3 disease and develop pulmonary infiltration, some of which will develop a very serious disease. So, the entire process starts when the virus infects the epithelial cells [7, 8].

Mortality in COVID-19

Based on the evidence and professional experience presently available, COVID-19 presents a greater risk for the elderly and individuals of any age who have specific underlying medical conditions. Older adults and those with chronic medical

conditions, including cancer, heart disease, diabetes, lung disease, and hypertension are at higher risk of experiencing more serious complications accelerated by COVID-19. As the number of COVID-19 infections continues to rise, a curious scenario has begun to emerge of otherwise healthy people succumbing to the virus. Experts are unable to determine clearly why the virus was fatal to some of the youngest patients, but has only led to mild symptoms in others. Mounting research suggests that most extreme cases are caused by aberrant immune responses and are not reliant on viral loads. This is where the epithelial cells should be considered an important mediator of the destructive process.

Epithelium and High-Risk Group

A brief overview of the epithelium for people with underlying diseases can provide us with various insights on COVID-19. Diabetes is coupled with increased glucose that distresses the respiratory epithelium, or vice-versa [9]. Similarly, several reports show increased epithelial expression of matrix metalloproteinases (MMPs) in lung tissue of COPD (chronic obstructive pulmonary disease) patients, demonstrating a role for the epithelial cell in alveolar destruction and airspace enlargement [10]. Any type of cancer starts its mutation or proliferation from the epithelial cells. In asthma, impaired epithelial proliferation is suggested to cause the bronchial epithelium which leads to increased secretion of profibrogenic growth factors [11]. Thus, the epithelium becomes damaged due to its underlying comorbidities. This may let the SARS-Cov-2 virus easily attach to the permeable epithelium.

Epithelium and Low-Risk Group

However, in the lower risk younger population, the epithelium permeability may be associated with alcohol intake, smoking, or stress. Long-term exposure to alcohol reduces the ability of the epithelial barrier to stand up against infection. Acute exposure to 0.2% or higher concentrations of ethanol has been shown to adversely affect epithelial cell interactions. It also reduces close junctions in epithelia and adheres to them [12, 13]. During their lifetime, mucosal epithelia encounter both physicochemical and biological stress. Several mechanisms have evolved to deal with stress, including regulation of immune cell functions. Also, numerous studies prove that psychological stress is associated with intestinal epithelial hyperpermeability [14–16]. Animal studies have shown that chronic and sporadic tobacco smoke exposure induces morphological alterations of the entire respiratory tract from hyperplasia to the epithelium [17]. This provides us an insight of the epithelium barrier interaction amongst those people without underlying comorbidities.

Epithelium Activation

The mucosal immune system is composed of locally synthesized polymer IgA. The polymers bind to the immunoglobulin receptors present on the basolateral surface of the mucosal epithelial cells. The polymer IgA receptor mediates transcytosis and endocytosis. IgA functions in host defense at three levels relative to the mucosal epithelium [18]. The epithelial cells influence the T and B cells by releasing chemokines. The epithelial cells also control the proliferation, activation, differentiation, and survival of T and B lymphocytes. The ability to resolve viral lung infections depends on interferon (IFN) and inflammatory cytokine actions of the epithelium. Epithelial activation is a characteristic feature of rhinitis, rhinosinusitis, a chronic obstructive pulmonary disorder, asthma, and other airway diseases. The inability of the epithelium to maintain a physical and immunological barrier may play a role in its susceptible nature to the diseases [19, 20].

Discussion

The capacity to overcome lung viral infections relies on interferon (IFN) and inflammatory cytokine activities, but their respective contributions to host protection and return to homeostasis remain unknown. Type III IFNs (IFN-λ) in particular have received a great deal of interest as they work mainly on mucosal surfaces [21]. Previous studies revealed that IFN-λ defends against viral infections and enhances the membrane roles of both intestinal epithelial cells and endothelial cells. Such differences can be clarified by the fact that in some experiments, the particular categories of cells attacked by IFN-λ were different. In fact, in a recent study finding by Broggi et al. [22], they reinforce the theory that IFN-λ adverse behavior happens even after prolonged contact and tissue harm exists. Perhaps, the early administration of IFN-λ in a COVID-19 mouse model conferred safety.

Conclusion

Considering that the epithelium provides essential host protection, it is rational to enhance their role during infection to improve outcomes. As suggested by Sharma et al. [23], strengthening the epithelial host defense can provide an important immunomodulatory strategy. Watching over epithelial immunity not only prevents collateral damage that can be caused by recruited immune cells but can also avoid the need to suppress these immune cells from the tissue [23]. Improving our understanding of epithelial functioning under normal and pathological conditions might provide new insights. There must be consistency in the system and there

may be more than one pathway. As we move forward in this field, novel pathways and factors will likely surprise us. The main focus will now be on supporting more in vitro or in vivo studies on this.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval Not applicable.

Informed Consent Not applicable.

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