Review Article

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Airway inflammation due to SARS-CoV-2

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Abstract:

Although there has been a large number of studies focusing on the role of airways in coronavirus disease 2019 (COVID-19), the relationship still remains unclear. With the disruption of the defense mechanism of the airways, including the intact mucus barrier, ciliary activity, and normal cough reflex, sticky and difficult-to-remove sputum becomes the main problem and the cough becomes the main symptom. Although interferons are considered the main elements of the defense against the virus, the pathogenesis of COVID-19 is complex and cannot be elucidated with only elevated interferon levels; there is more. The progression of the disease is mainly determined by the type and the levels of interferons and the affected part of the respiratory system. The airways have an important role in the pathogenesis of COVID-19, as the microorganism uses the airways as a gateway to the body, being the first element of defense against the virus, the importance of its relationship with the immune system, and its importance in the treatment.

Keywords:

Alveolar damage, interferon, pulmonary functions, respiratory distress, viral pneumonia

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has become the most popular issue of life in the new millennium. While most patients are asymptomatic or have mild symptoms, approximately one-fifth have serious illnesses requiring hospitalization, and one-fourth of them need intensive care unit (ICU) follow-up.[1] What makes patients more vulnerable to severe disease is unclear, but there are previously defined risk factors. COVID-19 patients who are older and have comorbidities, such as hypertension, diabetes mellitus, cardiovascular diseases, chronic lung diseases, chronic kidney disease, cancer, and obesity, are at higher risk of developing severe clinical outcomes than previously healthy individuals.[2]

Although it can affect almost all organ systems, the primary targets of the pathogen are the airways and lungs, utilized as

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gateways to the body. The virus may affect different compartments of the respiratory system and cause bronchitis, diffuse alveolar damage (DAD), and macro–micro thrombi in the pulmonary vasculature. In this review, we aimed to discuss a relatively unknown and unvalued issue, COVID-19-related airway inflammation.

Entrance Gate

The coronavirus family use angiotensin-converting enzyme-2 (ACE-2) to bind to the cell and carry on the pathogenesis.[3] The binding between ACE-2 and the spike (S) protein on the surface of the SARS-CoV-2 ensures the entry of the virus into the cell by activating transmembrane protease serine 2.[4,5] It means the higher ACE-2, the higher risk for severe infection. Wrapp et al.[6] showed that as a consequence of having more spike proteins, SARS-CoV-2 has more affinity to ACE-2 than SARS-CoV; thus, SARS-CoV-2 is a more dangerous virus than SARS-CoV.

Besides being the first organ system to encounter the virus, excessive ACE-2 expression on the bronchioles, alveoli, and vascular endothelium causes the respiratory system to be the main target of SARS-CoV-2.[7] In addition to the binding mission, ACE-2 has a balancing role by degrading angiotensin-2, which causes lung injury by its proinflammatory properties.[8,9] All these features make ACE-2 an issue of the pathophysiology and a treatment target for drugs and vaccines.

Clinical Phases of COVID-19

Binding to the cell surface is followed by endocytosis, amplification of viral genome by viral RNA-dependent RNA polymerase, and exocytosis.[10] Stage 1 (early phase) represents rapid virus replication and high viral load. In this phase, the clinical presentation is related to viral load and inflammation activates all host defense mechanisms to eliminate the pathogen. Alveolar macrophages invading the virus, activated T cells, and type 1 interferons play the antiviral role in this phase.[11] Laboratory findings are limited to mild lymphopenia. Fortunately, the war ends this phase in the majority, and patients suffer from mild illnesses.[12]

Stage 2, known as the "pulmonary phase," represents a transitional phase between the first stage and the hyperinflammatory third stage. This stage can be divided into 2a, which can be considered the end of the first stage, and 2b, where hyperinflammation begins. Besides, the local inflammation in the first phase spreads to the whole body by releasing inflammatory mediators into systemic circulation. Common laboratory findings are lymphopenia, the mild-to-moderate elevation of transaminases, and acute phase reactants, including C-reactive protein (CRP), sedimentation, and ferritin.[12] By this phase, shortness of breath and chest pain appear in addition to fever and dry cough.

The second part of the pulmonary phase is the precursor of stage 3, the hyperinflammation phase, in which autoimmunity plays the leading role while the activity of the virus is almost eliminated. Elevated proinflammatory cytokines and immune mediators such as interleukin 1 beta, interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor, tumor necrosis factor-alfa (TNF-α), and interferon-gamma (IFN-γ) activate more and more cells, which results in a vicious cycle.[11] All these processes cause a cell death called PANoptosis, which initiates a feedback loop that sustains lymphopenia, local edema, inflammation, and tissue damage.[11] Laboratory findings include increased acute phase reactants (CRP, lactate dehydrogenase, and ferritin), inflammatory markers (IL-1 and IL-6), and markers representing organ damage (troponin, n-terminal brain natriuretic peptide [NT pro-BNP], and creatinine). Patients have severe illnesses, such as acute respiratory distress syndrome, multiorgan failure, and shock.[12]

Airway Involvement

COVID-19 consequences on the lungs are airway disease, DAD, and thromboembolic events. Despite convincing data about alveolar and vascular involvement, the cause of COVID-19-related airway illness is still unknown. Airway involvement may result in increased airway secretion and nasal drip, which may cause only mild coughing, as well as thick viscous plugs that disrupt vital airway continuity and prevent ventilation.

The physical defense mechanism of the airways consists of an intact mucus barrier, a properly functioning ciliary activity, and a normal cough reflex. Sufficient mucus production is essential to protect the lungs from inhalation of toxic foreign particles and pathogens. However,

we should keep in mind that excessive accumulation of mucus is a crucial component of many respiratory disorders. Therefore, mucus expulsion from airways by mucociliary activity in harmony with production is also essential for normal function.[13]

Mucus hypersecretion and its tendency to be more viscous and thickness seem to be the major problem for airways. Widysanto et al.[14] reported that the bronchial walls were in normal appearance, but there was a thick and copious mucus plug in bronchi thought to result in desaturation in their bronchoscopies of COVID-19 patients. Mucus hypersecretion was also associated with typical radiologic findings of COVID-19. Numerous studies examining COVID-19 radiology explained ground-glass opacities (GGO) by partially filling the airspaces, air bronchograms by narrowing bronchi by gelatinous mucus, and bronchial wall thickening to hyperplasia of secretory cells.[15–17]

The mucus layer of the airway consists of two well-defined layers. The mobile gel layer, containing 98% water, is responsible for hindering penetration of the virus to the airway epithelium. The remaining 2% comprised mucin (MUC5B and MUC5AC) and other nonmucin components.[13,18] The other deeper and more concentrated layer is the stationary periciliary layer participating in mucociliary clearance.[19] Previous studies showed that several pathologic mechanisms cause excessive mucus production during viral infections. For instance, patients infected with influenza virus (IV) present with increased sputum and productive cough in which autopsy studies showed edema of the airway mucosa and accumulation of jealous material.[20,21] Another common infectious agent, respiratory syncytial virus, was shown to enhance mucus production, resulting in filling up bronchioles with thick plugs.[22,23] The closest relative of SARS-CoV-2, SARS-CoV, which typically causes DAD, has also triggered viscous mucus secretion.[24] Li and Tang have speculated that the SARS-CoV-2 may conduce similar pathological findings.[25] A study examining the bronchoscopies performed on 16 COVID-19 patients hospitalized in the ICU determined that the bronchoalveolar lavage of all patients was white-gray and highly viscous. Optical coherence tomography confirmed the mucus retention in bronchioles of COVID-19 individuals.[26] It was supported by autopsy studies that detected dense mucoid material in airways.[27–29]

Pathogenesis of Airway Inflammation

Role of interferons

In case a virus enters the respiratory tract, alveolar macrophages, T cells, and type 1 interferons take on the task of controlling the infection. This scenario works similarly with COVID-19. At this point, interferons (IFN) become important due to the role of clash with the virus by stimulating both IFN production by IFN producer cell (autocrine) and synthesis of IFN-regulated proteins (paracrine).[30] Type 1 IFN (IFN-1) and Type-3 IFN (IFN-3) induce interferon-stimulated genes (ISGs) to bring the immune system to "antiviral state." The ability of the virus to inhibit the release and the activity of IFN-1 determine whether the infection will be controlled at an early stage or viral load will increase rapidly and lead the disease to advanced stages.[31] However, Sposito et al.[32] argued that the issue is not that simple, and interferon levels in airways were measured in their study. They stated that higher IFN-3 and relatively lesser extent of IFN-1 levels in the upper respiratory tract in response to high viral load were associated with mild disease. But in contrast, overexpression of IFNs and low level of ISGs were also detected in lower respiratory tract of severe COVID-19 patients. Higher levels of IFN-3 in lower respiratory tract also result in the disruption of the protective barrier function of cells which may cause bacterial superinfections.[33] The role of interferons in COVID-19 defense seems to be a more complex mechanism related to the degree of viral load, anatomical localization, and age rather than a simple level increase.[32]

In summary, IFNs increase apoptosis and decrease proliferation acting as antiviral in acute infections, but type 3 IFNs play detrimental role in prolonged infections. Acting as antiviral in acute infections but in prolonged infections, type 3 IFNs play a detrimental role. Moreover, based on human and mouse model studies, upregulation of IFNs act as an antiviral/protective role in upper airways. When the virus reaches the lower airways, upregulation of type 3 and type 1 IFNs increases tissue damage and participates in hyperinflammatory response, which is detrimental.

Mucus hypersecretion

The main points of mucus hypersecretion are upregulation of the mucin gene and the stimulation of goblet cells, which contain secretory granules filled with mucin. Numerous mechanisms and substances are impelling the process, including (1) smoking: by producing reactive

oxygen species; (2) chronic obstructive pulmonary disease (COPD): stimulating TNF-α and epidermal growth factor receptor (EGFR); (3) asthma: interleukin (IL)-13-, IL-17-mediated allergic inflammation; and (4) infections.[34]

After the airway epithelium membrane recognizes the virus, the immune response, which will end with mucus hypersecretion, starts. Several soluble mediators and cytokines are secreted by epithelial, dendritic, and T helper-2 cells drive mucus secretion as a team. First, upregulation of IL-2, IL-4, and IL-6 enhances an increase in IL-5, IL-13, and TNF-α, which in turn causes the stimulation of IL-1β and IL-8. IL-4 and IL-8 use the activator of transcription (STAT) pathway to increase mucus secretion. Activation of STAT1, STAT3, STAT5, and STAT6 causes the upregulation of MUC5AC gene expression and mucus hypersecretion.[34,35]

Another pathway used by IL-1β, IL-5, IL-6, and IL-17 is mitogen-activated protein kinase. At the end of these pathways, where different intermediate substances are activated for each cytokine, there is an increase in MUC5AC gene expression and mucin production and secretion.[5,36,37]

Increased mucus hypersecretion by EGFR expression is led by TNF-α. TNF-α mediated by "nuclear factor kappa-light-chain-enhancer of activated B cells" protein complex causes overexpression of EGFR in the respiratory tract, concluding with MUC5AC gene expression and mucin production.[5,38]

The asthma-like leukotriene synthesis is also a possible pathway for COVID-19-related airway inflammation similar to rhinovirus. B cell activation by IL-2, IL-4, and IL-5 causes IgE production, mediating leukotriene production, and increasing mucus release.[5,35,39]

Effects on Pulmonary Function Tests

COVID-19 has long-term effects after the acute process, which is defined as "long COVID." Long COVID-19 symptoms include pulmonary system complaints such as shortness of breath, cough, exercise intolerance, and other organ systems such as fatigue, chest and abdominal pain, headache, difficulty in concentration, sleep disorders, diarrhea, and mood changes.[40] Pulmonary function tests (PFTs) are commonly used to determine whether there is a loss in pulmonary functions or not. Lewis and colleagues have investigated pre- and post-infection PFT results of 80 mild and moderate COVID-19 patients. They stated that there was no difference in forced expiratory volume at one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, total lung capacity, and diffusion capacity for carbon monoxide (DLCO). They also mentioned that there might be a relationship between underlying lung diseases and decreased lung functions after infection.[41] There were also studies examining changes in PFT parameters after discharge. Sonnweber et al.[42] investigated PFT results of 124 patients 3 months after discharge and stated that there was no abnormality in spirometry and static volumes but in DLCO. DLCO was normal in mild patients but significantly impaired in moderate and severe patients and correlated with the disease severity. In a recent prospective multicenter study, the most common PFT abnormality was DLCO decrease despite its severity decreasing over time. In their comprehensive review, Thomas et al.[43] stated that the most common PFT abnormality was DLCO compatible with interstitial extension radiologically. It seems that PFT abnormalities after COVID-19 are related to alveolar interstitium affecting DLCO rather than airways.

Conclusion

Although we have learned more and more about the pathogenesis of COVID-19 over time, we still have a knowledge gap about airway involvement. Local inflammation, edema, and increased secretion of viscous mucus causing narrowed airway seem to be the cornerstones of this issue. IFN expression in COVID-19 varies based on location, viral load, age, and severity. Enhanced eosinophil-mediated inflammation and dysregulated humoral responses might be the drivers of severe COVID-19. Future clinical, postmortem, and laboratory studies examining airway findings will enlighten us more on this issue.

Conflicts of interest
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References

1. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052–9. [CrossRef]
2. Rahman A, Sathi NJ. Risk factors of the severity of COVID-19: A meta-analysis. Int J Clin Pract 2021;75:e13916. [CrossRef]
3. Khan S, Siddique R, Shereen MA, Ali A, Liu J, Bai Q, et al. Emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2: biology and therapeutic options. J Clin Microbiol 2020;58:e00187–20. [CrossRef]
4. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271–80. [CrossRef]
5. Khan MA, Khan ZA, Charles M, Pratap P, Naeem A, Siddiqui Z, et al. Cytokine storm and mucus hypersecretion in COVID-19: review of mechanisms. J Inflamm Res 2021;14:175–89. [CrossRef]
6. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260–3. [CrossRef]
7. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586–90. [CrossRef]
8. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol 2019;316:H958–70.
9. Stanton BA, Hampton TH, Ashare A. SARS-CoV-2 (COVID-19) and cystic fibrosis. Am J Physiol Lung Cell Mol Physiol 2020;319:L408–15. [CrossRef]
10. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. JACC Basic Transl Sci 2020;5:518–36. [CrossRef]
11. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;27:1451–4. [CrossRef]
12. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405–7. [CrossRef]
13. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med 2010;363:2233–47. [CrossRef]
14. Widysanto A, Sutanto YS, Soetjipto AS, Lugito NP, Siahaan SS: Bronchoscopy Manifestation In Severe COVID-19 Patient: Case Series. Research Square Nov 06, 2020 [Epub ahead of print], doi: 10.21203/rs.3.rs-103263/v1. [CrossRef]
15. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol 2020;30:4381–9. [CrossRef]
16. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, et al. Chest CT findings in patients with coronavirus disease 2019 and its relationship with clinical features. Invest Radiol 2020;55:257–61. [CrossRef]
17. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol 2020;55:327–31. [CrossRef]
18. Thornton DJ, Rousseau K, McGuckin MA. Structure and function of the polymeric mucins in airways mucus. Annu Rev Physiol 2008;70:459–86. [CrossRef]
19. Hiemstra PS, McCray PB Jr, Bals R. The innate immune function of airway epithelial cells in inflammatory lung disease. Eur Respir J 2015;45:1150–62. [CrossRef]
20. Voskarides K, Christaki E, Nikolopoulos GK. Influenza virus-host co-evolution. A predator-prey relationship? Front Immunol 2018;9:2017. [CrossRef]
21. Taubenberger JK, Morens DM. The pathology of influenza virus infections. Annu Rev Pathol 2008;3:499–522. [CrossRef]
22. Rossi GA, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: respective role in inception and persistence of wheezing. Eur Respir J 2015;45:774–89. [CrossRef]
23. Lee N, Lui GC, Wong KT, Li TC, Tse EC, Chan JY, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis 2013;57:1069–77. [CrossRef]
24. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet 2003;361:1773–8. [CrossRef]
25. Li Y, Tang XX. Abnormal airway mucus secretion induced by virus infection. Front Immunol 2021;12:701443. [CrossRef]
26. Lu W, Liu X, Wang T, Liu F, Zhu A, Lin Y, et al. Elevated MUC1 and MUC5AC mucin protein levels in airway mucus of critical ill COVID-19 patients. J Med Virol 2021;93:582–4. [CrossRef]
27. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis 2020;20:1135–40. [CrossRef]
28. Liu Q, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, et al. Gross examination report of a COVID-19 death autopsy. Fa Yi Xue Za Zhi 2020;36:21–3.
29. Farooqi FI, Morgan RC, Dhawan N, Dinh J, Yatzkan G, Michel G. Airway hygiene in COVID-19 pneumonia: treatment responses of 3 critically ill cruise ship employees. Am J Case Rep 2020;21:e926596.
30. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001;14:778–809. [CrossRef]
31. Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, et al. Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe 2020;27:883–90. [CrossRef]
32. Sposito B, Broggi A, Pandolfi L, Crotta S, Clementi N, Ferrarese R, et al. The interferon landscape along the respiratory tract impacts the severity of COVID-19. Cell 2021;184:4953–68. [CrossRef]
33. Broggi A, Ghosh S, Sposito B, Spreafico R, Balzarini F, Lo Cascio A, et al. Type III interferons disrupt the lung epithelial barrier upon viral recognition. Science 2020;369:706–12. [CrossRef]
34. Dickey BFK, Knowles MR, Boucher RC. Mucociliary clearance. In: Grippi MA, Elias JA, Fishman JA, Kotloff RM, Pack AI, Senior RM, et al, editors. Fishman's Pulmonary Diseases and Disorders. 5th ed. McGraw Hill; 2015. p. 93–103.
35. Saris A, Reijnders TDY, Nossent EJ, Schuurman AR, Verhoeff J, Asten SV, et al; ArtDECO consortium and the Amsterdam UMC COVID study group. Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19. Thorax 2021;76:1010–9.
36. Yu H, Li Q, Kolosov VP, Perelman JM, Zhou X. Interleukin-13 induces mucin 5AC production involving STAT6/SPDEF in human airway epithelial cells. Cell Commun Adhes 2010;17:83–92. [CrossRef]

37. Burgos-Blasco B, Güemes-Villahoz N, Santiago JL, Fernandez-Vigo JI, Espino-Paisán L, Sarriá B, et al. Hypercytokinemia in COVID-19: Tear cytokine profile in hospitalized COVID-19 patients. Exp Eye Res 2020;200:108253. [CrossRef]
38. Kankaanranta H, Ilmarinen P, Zhang X, Adcock IM, Lahti A, Barnes PJ, et al. Tumour necrosis factor-α regulates human eosinophil apoptosis via ligation of TNF-receptor 1 and balance between NF-κB and AP-1. PLoS One 2014;9:e90298. [CrossRef]
39. Xue L, Barrow A, Fleming VM, Hunter MG, Ogg G, Klenerman P, et al. Leukotriene E4 activates human Th2 cells for exaggerated proinflammatory cytokine production in response to prostaglandin D2. J Immunol 2012;188:694–702. [CrossRef]
40. CDC. Post-COVID conditions. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed Oct 20, 2021.
41. Lewis KL, Helgeson SA, Tatari MM, Mallea JM, Baig HZ, Patel NM. COVID-19 and the effects on pulmonary function following infection: A retrospective analysis. EClinicalMedicine 2021;39:101079.
42. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J 2021;57:2003481.
43. Thomas M, Price OJ, Hull JH. Pulmonary function and COVID-19. Curr Opin Physiol 2021;21:29–35. [CrossRef]