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Review Article

Immune Response to COVID-19: Understanding the Lethal Pandemic

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Abstract

The SARS-CoV-2 virus causes COVID-19, a severe respiratory disease that can lead to death. The virus primarily invades the lungs' epithelium, specifically the pneumocytes. Mild infections are often asymptomatic, while severe infections result in various respiratory distress depending on the host's immune response, which varies by age. The present article explores the impact of COVID-19 on infected lungs and the innate and acquired immune responses involved. Alveolar and interstitial macrophages, monocytes, neutrophils, dendritic cells, natural killer cells, and T and B lymphocytes contribute to the specific immune response. Additionally, the article briefly discusses dendritic cells' role as professional antigen-presenting cells and the main interferon-producing signal in response to SARS-CoV-2, type I IFNs. Lastly, it provides a brief overview of vaccine development, a critical aspect of combating the infection.

Keywords: Amphiregulin, Bronchoalveolar lavages, COVID-19, Desquamation, Edema, Lymphopenia, Megakaryocytes, Myeloid, Thrombocytes, Thrombocytopenia.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a single-stranded positive-sense RNA virus that belongs to the Coronaviridae family in the genus Beta coronavirus of the Orthornavirae Kingdom. This virus has caused a troublesome global pandemic that has resulted in the deaths of millions. The clinical manifestations of COVID-19 range from the asymptomatic or mild symptoms stage to severe stages of acute respiratory illness or respiratory failure. In the mild stage, symptoms such as cough, fever, and breathing problems are observed, while in severe cases, pulmonary edema, hyaline formation, and pneumocyte desquamation are observed.

The SARS-CoV-2 virus primarily invades human lung epithelial cells, making them one of the first targets. The virus is transmitted through droplets, which primarily infect upper airway epithelial cells that are rich in Angiotensin Converting Enzyme 2 (ACE2) viral receptors, leading to subsequent spreading to the lower airways in severe cases. Pulmonary pathology has been defined as diffused alveolar damage (DAD) and subsequent Acute Respiratory Distress Syndrome (ARDS) with severe and frequent thromboembolic complications with intravascular fibrin deposition. The systemic manifestations of the virus result from delayed immune response against the infection and a lack of knowledge about the virus and the immune response generated against it. The severity of COVID-19 correlates with comorbidities such as older age, cancer, pneumonia, obesity, cardiovascular disease, diabetes, immunosuppression, and lung-related problems. The immune response against COVID-19 is an outcome of both innate and acquired immunity (Melenotte et al., 2020; Szekely et al., 2021).

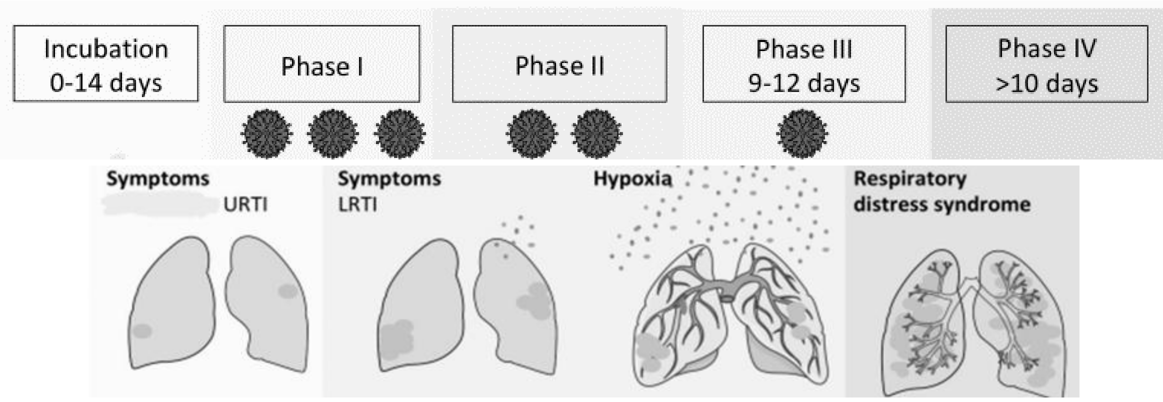

Fig-1: Natural history of COVID- 19 Infection

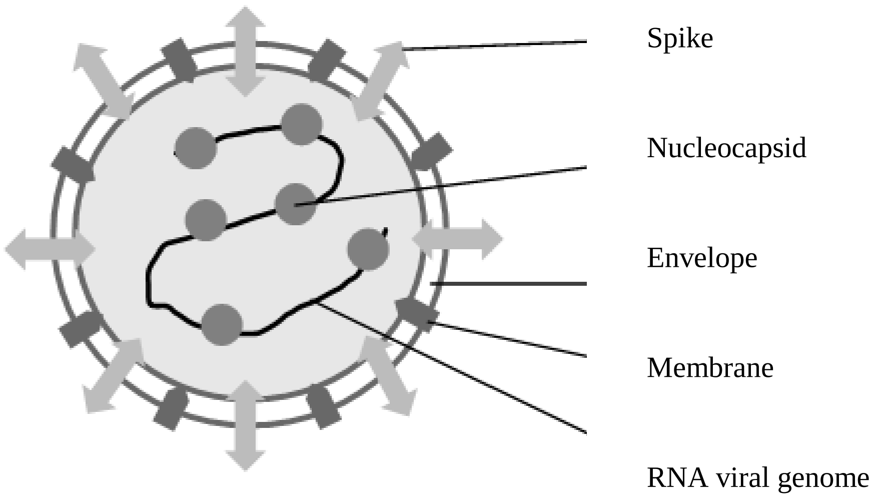

Fig: Structure of SARS-Cov-2

The corona virus structure is crown like having spikes on their surface in Latin this type of structure is called "Corona". Based on the structure of their genome they are divided into alpha, beta, gamma and delta subgroups out of which alpha and beta infect mammals. They are pleomorphic and enveloped (lipid protein) having positive sense single stranded RNA with RNA polymerase of size nearly 29.9kb having 6 extra open reading frames (ORFs) in genome. The genome code for four main structural proteins which are nucleocapsid protein, spike protein, envelope and membrane protein. Viral genome also codes for several non-structural proteins. Out of four structural proteins spike proteins identify host and enable virus to attach on specific receptors which poses various receptor binding domains which binds to AEC-2. Protease enzyme of host cell dissolve the viral membrane due to which RNAs are released into host cell taking over cell machinery and inhibiting immune response by producing virulence factors (Hosseini et al., 2020, King et al., 2020, Boopathi et al., 2021)

Anatomy of lungs of the infected person

The lungs are complex and important organ with specialised structure made for exchange of gases to fulfil the oxygen demand and release out carbon di oxide from human body. The study of abnormalities in lungs of COVID-19 patients is important as it is the main damaged organ due to infection. The lungs are divided into upper and lower respiratory tract containing structures like bronchioles and alveoli. The COVID- 19 infection initially takes place in upper respiratory tract of lungs and gradually spread in lower respiratory tract (Melenotte et al., 2020, Wang et al., 2020).

According to Szekely L et al. study, the lungs of infected persons were heavy and fluid filled, approximately 2.8 times heavier than normal lungs. Lungs of infected persons were firm to touch with rubbery consolidations. Lungs had negligible air content. The posterior part of the lower lobes of lungs were free from air and were fully consolidated (Szekely et al., 2021).

The mucous membranes of most of the patients were found unaffected. But some patients show purulent trachea bronchitis and some shows blood filled swollen mucous membrane. (Szekely et al., 2021).

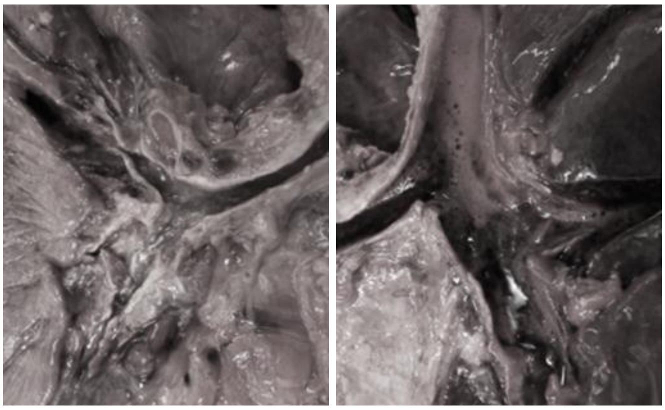

Fig: 3. Purulent tracheal bronchitis (left); Blood filled swollen mucous membrane (right)

The most severe pathological change that occurred in the lung parenchyma started with immense cytopathogenic effects on both Type I and Type II pneumocytes. On infection the pneumocytes were very much swollen and assembled as single cells. The damaged alveoli were often filled with edema fluid, plasma, coagulated fibrin, blood or coagulated blood and cells like macrophages, neutrophils and lymphocytes. The viral RNA mostly replicates in pneumocytes. The desquamated pneumocytes regularly showed advanced cellular abnormalities/atypia with nuclear heterogeneity and unusual and strange shaped cytoplasm. Due to these abnormalities in cellular structure pneumocytes were casually demonstrated as “COVID cells”. The regular denudation of the alveolar wall was often accompanied with the damage of the alveolar capillaries and release of plasma and blood into the alveolar space resulting in infection of alveolar epithelial cells. Diffuse alveolar damage in the patients of COVID- 19 was observed due to massive production of hyaline membrane structure which contained residues of the debris of alveolar epithelial cells, macrophages and serum proteins. (Szekely et al., 2021, Wang et al., 2020, Aguiar et al., 2020).

Large intra vascular thrombus formation in branches of pulmonary arteries was observed in some cases which were composed of aggregated thrombocytes. The conditions like trachea bronchitis/ pneumonia are observed induced by viral infection and aggravated by bacterial superinfections. Lung consolidation was accompanied with the accumulation of large number of macrophages and immature myeloid elements along with substantial proliferation in both epithelial and stomal components. The central part of lungs was mainly affected due to infection in comparison to peripheral parts which were less affected (Szekely et al., 2020, Aguiar Diego et al., 2020).

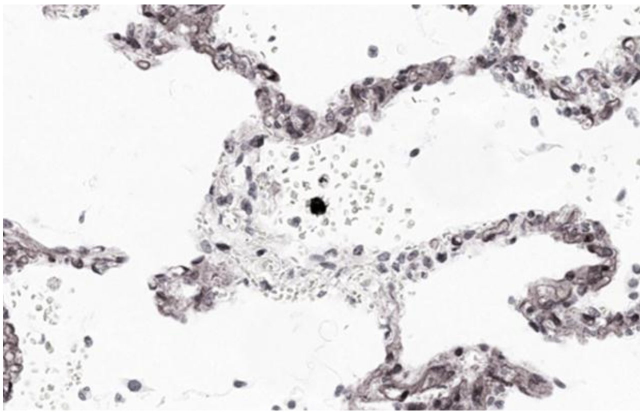

Fig-4: Damage of alveolar capillary wall due to COVID- 19 infection that led to intra alveolar bleeding

Immune response produced against COVID-19 Infection

Innate Immune Response

Pulmonary innate lymphoid cells (ILCs) play important role in mitigating viral infection in lungs. Following types of ILCs take part in producing immune response against COVID-19 infection:

1. Macrophages

Pulmonary macrophages maintain lung homeostasis by clearing dead cells and invading pathogens and phagocytose the pathogen cells. There are two different types of macrophages present in lungs: (i) The Alveolar Macrophages (AMs) and (ii) Interstitial Macrophages (IMs). The AMs arise mostly from fatal hepatic monocytes. The IMs are located with dendritic cells and lymphocytes in the interstitium. IMs are of two types: CD206+ which are tolerogenic and secretes chemokine and CD206- which acts as antigen presenting cells. A unique subset of IMs known as “Nerve airway macrophages” (NAMs) mitigate viral infection through Interleukin-10. Broncho-alveolar lavages (BALs) from patients having sever infection contained more macrophages. Pulmonary macrophages specifically AMs can control resident memory T cells (TRMs) of lungs. TRMs are perfectly positioned against respiratory pathogen such as corona virus. Viral infection of epithelial cells leads to the activation of macrophages and dendritic cells which secret IL-12, IL-18 and type I-INF along with-it activating NK cells to exert effector function. Damaged epithelium sensed by AMs releases IL-25, IL-33 and TSLP alarmins acting on ILC-2 to stimulate their proliferation and effector function. ILC-2 derived amphiregulin (AREG) which is widely expressed transmembrane tyrosine kinase promote epithelial cell repair (Melenotte C et al., 2020).

2. Monocytes

Monocytes are haematopoietically derived innate immune cells whose function ranges from inflammatory to anti-inflammatory response. They are classified as classical (CD14high), non-classical (CD16high) and intermediate monocytes (CD14+CD16-). During COVID-19 CD14+ monocytes are overactivated which results in emergence of monocytic subsets including myeloid derived suppressor cells (MDSC) with in COVID-19 patients (Mukund et al., 2021).

3. Low-Density Neutrophils

It is the term used for heterogenous group of different types of neutrophil cells composed of a mixture of immature and low-density mature neutrophils, progenitor cells and granulocytic/ polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs). Low density neutrophils are highly proliferative and activated mostly in severe COVID-19 cases. Low density granulocytes are significantly proinflammatory and interferon-1 responsive. PMN-MDSCs play important role in the immune dysregulation in severe COVID-19 infection cases. Megakaryocytic expansion in severe COVID-19 cases also reported. Thrombocytopenia is associated with increased platelet demand and exhibit emperipolesis observed in COVID-19 cases is fulfilled by Megakaryocytes. (Mukund et al., 2021).

4. Natural Killer Cells

NK cells are non-phagocytic lymphocytes that respond rapidly to eliminate or control pathogens in host cell including tumour progression, microbes and viruses. During COVID-19 activation of NK cells with impaired cytolytic/osmotic lysis potential and reduced absolute cell counts, with increased severity in infection was reported. NK cells also show increased interferon signalling with increased expression of the inhibitory surface protein in moderate and sever patients (Mukund et al., 2021).

Acquired Immune Response

Acquired/Adaptive immunity is crucial for successful viral clearance and long-term immunity.

1. T cells

Virus clearance during a primary response induced against COVID-19 infection depends on coronavirus virus specific CD4+ and CD8+ T cell response. Compared with healthy individuals, the number of T-cells were reduced in severe COVID-19 patients. Higher proportion of CD8T/CD4T effector cells are observed in higher proportions in non-severe subjects as compared to healthy individuals but this number decreases with increase in severity. An increase in CD8T effector and CD4t naïve cells is reported in patients with non-severe subjects. In addition to this increase in CD4+ Tregs was also reported which are crucial for regulating immune homeostasis and autoimmunity, controlling the quality and magnitude if immune response. The cluster CD16+CDT8 subset showed significant increase in proportion of cells within both severe and non-severe COVID-19 patients. A notable decrease in cellular abundance of low frequency T subsets including Mucosal Associated Invariant T and Gamma Delta T cells was seen in COVID-19 individuals. MAITs are class of non-conventional T cells and respond to innate inflammatory signals including IL-12, IFN-γ and IL-18 with viral infection including COVID-19. Despite low abundance MAIT cells in severe and non-severe disease showed increased activation. T cell Lymphopenia include a sustained type I INF response and high level of stress-induced glucocorticoids together contributing to T cell apoptosis (Qin et al. 2020, Melenotte et al., 2020, Mukund et al., 2021).

2. B cells

B cells are observed to produce immune response against COVID-19 infection. The B cells play a crucial role against SARS CoV-2 by producing immunoglobulins that provide protection against protection from mild disease to severe stage. Immature B cells mature to naïve B cells and proliferate into memory cells and plasma B cells upon antigenic activation. With increase of severity B cell dysfunction with decrease in multiple cell types including naïve B cells is observed. Plasma B cells exceptionally showed expansion and heterogeneity with increasing disease severity. Exceptionally increase in Plasma B cells concentration is observed with increase in severity of infection (Qin et al.2020, Melenotte et al., 2020, Mukund et al., 2021).

Antigen Presenting Cells (APCs)

Classical Dendritic Cells (cDCs) acts as professional APCs that initiate and regulate the pathogen specific adaptive immune response by providing antigen for proliferation of lymphocytes and production of antibodies and associated factors. cDSc can be subdivided into cDC1 and cDC2 based on their expression of cell surface markers, gene expression profile, specific transcription factor required for their development and unique functions. During COVID-19 infection decrease in APCs is reported resulting decrease in DC subsets favouring lymphopenia. Highly polarized human lung epithelial cells infected by SARS-CoV-2 can modulate the intrinsic functions of monocyte-derived macrophages and dendritic cells (DC) respectively. They slow down the APC functions of DC and macrophage phagocytosis through a mechanism involving IL-6 and IL-8. In contrast, cDC1 resist to most viral infections, thereby maintaining their APC functions through their constitutive expression of vesicle trafficking protein RAB15 (Melenotte et al., 2020).

Interferons

Type I interferons is main INF signalling during COVID-19 which includes INF-α, β and ω cytokines, producing cellular antiviral response through the JAK-STAT signalling pathway and through the induction of interferon stimulated genes (ISGs). An impaired type I IFN response was observed in severe COVID-19 infection cases. Patient with low type I IFN plasma level reported high blood viral load. Human coronavirus encodes multiple structural and non-structural proteins that antagonize IFN and ISG response. Genetic factors may influence the IFN response and explain the individual variability in antiviral response. Pathogen associated molecular patterns (PAMPs) such as ssRNA or viral protein in case of COVID-19 trigger the activation of transcription factor leading to pro inflammatory cytokine and type I IFN induction. Viral replication is actually accompanied by a delayed type I IFN signalling that produce inflammatory responses and lung immunopathology. Type I IFN remained detectable until after the peak of viral titres, and delayed IFN-I signalling promoted recruitment of pathogenic inflammatory monocytes/macrophages, resulting in vascular leakage and impaired virus-specific T cell response (Melenotte et al., 2020).

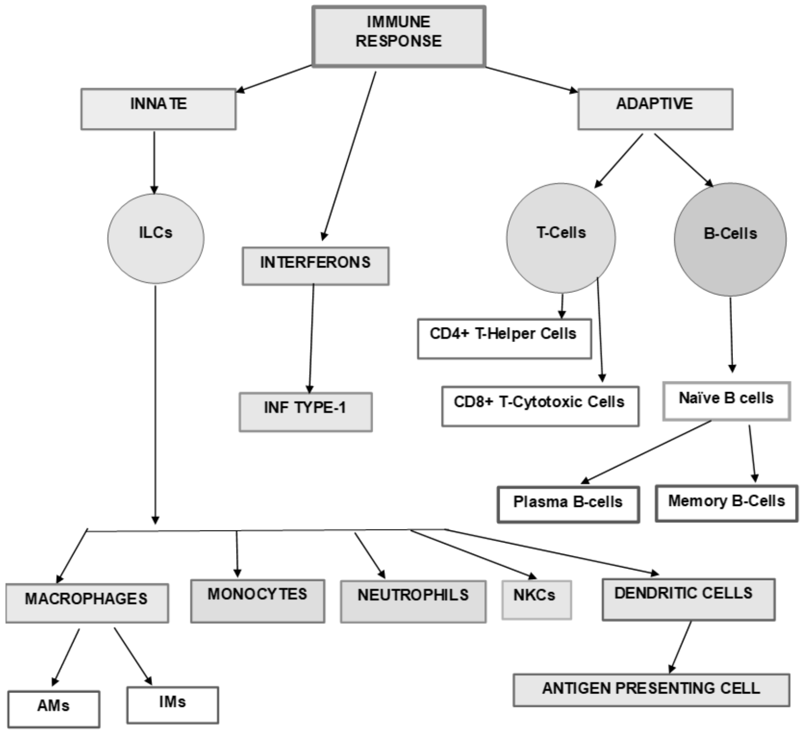

Fig-5: Immune Response during Covid-19 flow chart

Vaccination

The idea behind vaccination is to expose the host body against the antigen that will not cause disease but will provide immune response against viral infection.

There are ongoing trails and development of vaccines mainly based on four broad types which are Protein Based Vaccines (PBVs), Virus Like Particles Vaccines (VLPs), Nucleic Acid Vaccines (NAVs) and Virus Vector Vaccines (VVVs). In PBVs direct injection of viral protein into host or injection of viral antigens developed from recombinant protein techniques take place. In VLPs weaker or inactive form of virus or self-assembled virus protein structure lacking viral genome is induced in host body. From NAVs proteins are developed or gene encoding viral antigenic components that are expressed by plasmid vector induced into host cell. In VVVs virus like adeno virus is genetically engineered to provide antigens for immune response against target virus. There are several vaccines developed based on various factors like eGFP-SARS-COV-2 which precent binding of virus at ACE2 receptors, recombinant adenovirus type-5 vaccine & BNT162b1 vaccine which produce antibodies against the virus and live attenuated vaccines which are considered as successful vaccines (Li et al., 2020, Melenotte et al., 2020).

Conclusion

The COVID-19 infection served as most deadly pandemic to whole human kind. The disease had great impact on global health care system due to lack of knowledge about the life cycle of virus, detection and prevention measures. COVID-19 had a great impact on respiratory systems of infected individuals initially which later resulted into serious health problems or death. Study of both virus infection induced cell damage and response of hosts of different age group should take place, as most of the deaths were of old age individuals.

Both innate and adaptive immune response immune responses induced virus clearance, inhibited virus replication and promoted tissue repair mechanism.

Both the type of immune responses and their interaction with interferons should be studied comprehensively. There is an urgent need for a high dimensional longitudinal follow up of the underlying immunological mechanisms across the different stages of the COVID-19 to make more rational and personalised therapeutic decisions. The current goal should be development of broad range of effective vaccines against coronavirus keeping in mind of different strains of the virus which are generated due to mutation.

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References

- Aguiar, D., Lobrinus, J. A., Schibler, M., Fracasso, T., & Lardi, C. Inside the lungs of COVID-19 disease. International journal of legal medicine (2020), 134, 1271-1274.; https://doi.org/10.1007/s00414-020-02318-9
- Boopathi, S., Poma, A. B., & Kolandaivel, P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. Journal of Biomolecular Structure and Dynamics (2021)., 39(9),3409-3418. https://doi.org/10.1080%2F07391102.2020.1758788
- Hosseini, A., Hashemi, V., Shomali, N., Asghari, F., Gharibi, T., Akbari, M, et al. Innate and adaptive immune responses against coronavirus. Biomedicine & pharmacotherapy (2020) , 132, 110859.
- King, J., Collins, M., Sundberg, E. Coronavirus Structure, Vaccine and Therapy Development. MIT publication (2020); Vol. XXXII No.04.
- Li, Y. D., Chi, W. Y., Su, J. H., Ferrall, L., Hung, C. F., & Wu, T. C. Coronavirus vaccine development: from SARS and MERS to COVID-19 .Journal of biomedical science (2020). , 27(1), 1-23.https://doi.org/10.1186/s12929-020-00695-2
- Melenotte, C., Silvin, A., Goubet, A. G., Lahmar, I., Dubuisson, A., Zumla, A.,et al,.Immune responses during COVID-19 infection. Oncoimmunology (2020), 9(1), 1807836.
- Mukund, K., Nayak, P., Ashokkumar, C., Rao, S., Almeda, J., Betancourt-Garcia, M. M., et al. Immune response in severe and non-severe coronavirus disease 2019 (COVID-19) infection: A mechanistic landscape. Frontiers in immunology (2021), 12, 738073.
- Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases (2020), 71(15), 762-768.
- Szekely, L., Bozoky, B., Bendek, M., Ostad, M., Lavignasse, P., Haag, L., et al. Pulmonary stromal expansion and intra-alveolar coagulation are primary causes of COVID-19 death. Heliyon (2021), 7(5), e07134.
- Wang, C., Xie, J., Zhao, L., Fei, X., Zhang, H., Tan, Y.,et al. Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. EBioMedicine (2020). 57,102833: https://doi.org/10.1016/j.ebiom.2020.102833.