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Interplay between hypoxia and inflammation contributes to the progression and severity of respiratory viral diseases

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ABSTRACT

History of pandemics is dominated by viral infections and specifically respiratory viral diseases like influenza and COVID-19. Lower respiratory tract infection is the fourth leading cause of death worldwide. Crosstalk between resultant inflammation and hypoxic microenvironment may impair ventilatory response of lungs. This reduces arterial partial pressure of oxygen, termed as hypoxemia, which is observed in a section of patients with respiratory virus infections including SARS-CoV-2 (COVID-19). In this review, we describe the interplay between inflammation and hypoxic microenvironment in respiratory viral infection and its contribution to disease pathogenesis.

1. History of viral pandemics

History of pandemics is dominated by viral diseases. In the first half of 400 BCE, the Greek physician Hippocrates described a malaise with symptoms similar to that of influenza for the first time (Barberis et al., 2016). The first influenza pandemic was reported in 1510. Influenza pandemics have become a recurrent event at a frequency of every 10–30 years due to its varied subtypes (Potter, 2001). The Russian Flu pandemic of 1889 had claimed lives of about 1 million people worldwide (Noor and Maniha, 2020). The Spanish flu of 1918 had affected more than 50 million lives around the world (Noor and Maniha, 2020; Saunders-Hastings and Krewski, 2016). The 1957 Asian Flu, first identified in China and caused by H2N2 subtype, had caused two million deaths globally (Noor and Maniha, 2020; Saunders-Hastings and Krewski, 2016). The 1968 Hong Kong Flu, caused by H3N2 subtype had proved to be fatal for almost one million people around the world (Noor and Maniha, 2020; Saunders-Hastings and Krewski, 2016). The 2009 Swine Flu, caused by H1N1 subtype was first detected in Mexico. It is estimated that mortality due to this pandemic may be ranging from 150 to 500 thousand (Morens et al., 2020; Saunders-Hastings and Krewski, 2016). The latest disease in this list is Coronavirus disease 2019 (COVID-19). It is caused by newly identified strain that was for the first time detected in Wuhan, China in latter half of December of 2019. The nomenclature of this strain is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Until the discovery of pathogenic strain of SARS, coronaviruses were considered to possess low pathogenicity among the family of viruses. Global case fatality rate for SARS-CoV-2 is estimated to be approximately 3.31% (Cao et al., 2020). It is now clear that they are highly adaptive in nature and therefore potential pathogens (Lauer, 2020). As of May 4, 2021, the total number of cases stand at 154,195,608 and has caused 3,227,188 deaths globally (Worldometer, 2021).

2. Viral infection

Virus is a sub microscopic infectious agent with a diameter ranging from 20 to 300 nm. Its genetic material can be either RNA or DNA, encapsulated in a proteinaceous coat called the capsid (Gelderblom, 1996). Several viruses also have an additional phospholipid layer, called the envelope. A viral particle cannot replicate by itself. Viruses infect cognate host cells and utilize its components for replication and propagation (Fast, 1999). Often, the host cells die in this process therefore causing adverse complications in the host organism. The replicative life cycle of a virus depends on the host as well as the virus family. However, few basic steps are common amongst all viruses. Viral proteins on the capsid or on the envelope bind to specific receptors on the host cell surface. Envelope free viruses directly penetrate into the cell. While, enveloped viruses first fuse with plasma membrane and then releases the nucleocapsid (Dimitrov, 2004). The uncoating of the capsid releases the viral genome into the cell for replication and transcription followed by
production of viral proteins. Genesis of new capsids takes place hereafter and the newly replicated genetic material is then packaged into these capsids. New virion particles are then released, which can infect new host cells. The probability of mutation in the genetic material of viruses is usually very high. This generates a wide array of strains with varying degrees of virulence (Rajcani, 2003). Mutation rate of a virus also determines the ability of a virus to escape the host immune system and imparts it evolutionary advantage to survive and propagate with the passage of time (Sanjuan et al., 2010).

3. Immune response to viral infection

Virus infected cells are not directly recognised and eliminated by cell mediated immunity. Host cells use a protein complex called the major histocompatibility complex class I (MHC class I) to display short stretches of foreign protein inside the cell on the cell surface. If a cell is infected with a virus, these peptides include fragments of proteins of viral origin. The cytotoxic T cell then recognizes and kills the infected cells with the help of Perforin and Granzyme B (Sewell et al., 2000). The virus infected leukocytes secrete small proteins called interferons, which play a crucial role in imparting protection against viruses (Lee and Ashkar, 2018). The Toll-like receptors (TLRs) present on cell surface (TLR1, TLR2, TLR4, TLR6) and in the cytoplasm (TLR3, TLR7/8, TLR9) also assist in viral protein and genetic material recognition respectively (Lester and Li, 2020). The intracellular TLRs upon binding to viral DNA or RNA produce interferons which prevent replication of viruses (Boehme and Compton, 2004).

Besides, viral infection can activate B lymphocytes to produce antibodies through activated helper T lymphocytes. The viral antigens are also presented by MHC class II molecules to naive Helper T cells by antigen presenting cells, especially dendritic cells. Activated Helper T cells now interact with B cells to differentiate them into rapidly proliferating plasmablasts and eventually non-dividing plasma cells. Production of antigen-specific immunoglobulin IgG, IgM, and IgA after clonal expansion of plasmablasts help in the generation of pool of virus specific antibodies (Baumgarth, 2014; Lam and Baumgarth, 2019). Antibodies neutralise viral particles which are then easily engulfed and eliminated by phagocytic cells (Laing and Hutchinson, 2008). Antibodies can also bind to the infected host cells and direct its lysis by the complement system (Agrawal et al., 2017).

Upon viral infection, cells of the first line of defence i.e. monocytes, macrophages, neutrophils and dendritic cells secrete inflammatory cytokines, present antigen and chemokines, which function to eliminate the infection. This review primarily focuses on inflammatory response to viral infections.

4. Inflammation in viral infection

Host immune system recognizes and destroys the virus and virus infected cells. The innate immune cells including monocytes, macrophages, DCs and neutrophils exhibit phagocytic activity and can engulf virus and virus infected cells and also secrete inflammatory cytokines and chemokines that protect new cells from infection.

Interferons (IFN), one of the bioactive molecules released by these cells helps in eliciting precise immune response to the invading virus. The type-I and type-III IFNs are secreted by many cell types upon infection whereas type-II IFN is mainly secreted by immune cells such as NK cells and T cells. Type-I interferons IFN-α and IFN-β are an important part of the treatment regime for patients with chronic hepatitis B and C viruses. Generally, IFN-α is produced by leukocytes and IFN-β is produced by fibroblasts (Lia, 2018). Type 1 interferons work through paracrine, autocrine as well endocrine modes. They are known stimulators of antiviral gene expression and can dampen viral replication in cells. Enhancement of MHC II expression, antigen presentation, upregulation of co-stimulatory molecules and maturation of dendritic cells are driven by Type I interferons (Lee and Ashkar, 2018).

Recognition of viral immunogen by airway epithelial cells or immune cells causes NF-κB pathway dependent expression of inflammatory cytokines, chemokines and growth factors. Activation of IL-1 family of cytokines requires activation of inflammasome complex NLRP3 to enzymatically cleave and activate the pro-cytokine to active cytokine for downstream effects (Zhao and Zhao, 2020).

Inflammatory response elicited by different viruses are different and involves various types of inflammasomes including the absent in melanoma 2 (A2M2), NLRP3, the γ-interferon-inducible protein 16 (IFI16) and RIG-I (Table 1). Several viruses such as mouse cytomegalovirus (MCV), human papillomavirus, hepatitis B virus (HBV), HIV, influenza virus and vesicular stomatitis virus (VSV), vaccinia virus (VACV) have been reported to activate the inflamasomes (Kumar et al., 2018). Inflammasome activation at early stages of infection is important for efficient immune response and protection from severity. It is presumed that Influenza virus activates the inflammasome through NF-κB (To et al., 2019). However, prolonged activation of the inflammasome can add to disease severity. SARS-CoV has also been reported to activate NLRP3 inflammasome assembly by three different proteins. SARS-CoV open reading frame (ORF) 3a protein can generate mitochondrial ROS and K⁺ efflux leading to activation of NLRP3 inflammasomes (Zhao and Zhao, 2020).

Table 1

| Pathogens                  | Pattern Recognition Receptor | Cytokines’ expression modulated | References                          |
|----------------------------|-------------------------------|---------------------------------|-------------------------------------|
| KSHV, EBV, HSV-1           | IFI16                         | Type I IFNs, IL-1               | Ansari et al., 2013                 |
| Influenza virus, HCV, Babes virus, JEV | RIG-I                         | Type I IFNs, IL-1               | Ansari et al., 2015                 |
| VACV, HBV, HPV and mCMV    | AIM2                          | IL-1β and IL-18                 | Kato et al., 2005; Loo et al., 2008 |
| Influenza virus, Sendai virus, Vaccinia, Rabies Virus, encephalomyocarditis virus (EMCV) and vesicular stomatitis virus (VSV) | NLRP3                         | IL-1β and IL-18                   | Horning et al., 2009; Reinholz et al., 2013; Wu et al., 2013 |
| SARS Co-V                  | NLRP3                         | IL-1β and IL-18                 | Allen et al., 2009; Lawrence et al., 2013; Rajag et al., 2011 |

SARS-CoV protein nsp 1, nsp 3, ORF3b, ORF6 and ORF9b can induce NLRP3 expression (I. Chen et al., 2011; Siu et al., 2019; Ansari et al., 2015; Lawrence et al., 2013; Wu et al., 2013). On the other hand, SARS-CoV proteins nsp 1, nsp 3, ORF3b, ORF6 and ORF9b are reported to suppress interferon production in order to dampen the antiviral response (Channappanavar and Perlman, 2017).

Respiratory viruses pose the highest risk of severity and mortality due to the respiratory system’s role in oxygen exchange and circulation. Common respiratory viruses include influenza virus rhinoviruses, influenza virus respiratory syncytial virus (RSV), human metapneumovirus and parainfluenza viruses (Schwarz and Mackenzie, 2013). Airway epithelial cells and mucosal immune cells are usually the first ones to get infected. Upon getting infected these cells elicit immune response by recognizing viral genetic material and viral surface protein through array of receptors and sensors. Thus, type I IFNs, inflammatory cytokines and chemokines via NF-κB transcription factor activation are released (Li et al., 2019; Schwarz and Mackenzie, 2013). This pre-initiation response lays foundation for the subsequent extent of disease progression and also determines the nature of immune response (Li et al., 2019).
5. Interplay between hypoxia and inflammation in viral infection

Interplay between hypoxia-induced inflammation and inflammation-induced hypoxic microenvironment usually aggravates morbidity in respiratory disease. Inflammation can increase the activation of hypoxia inducible factors via distinct mechanisms. TNF-α increases HIF-1α stabilization through NF-κB (Jung et al., 2003a; Zhou et al., 2003), TGF-β enables accumulation of HIF-1α by inhibiting prolyl hydroxylase 2 (PHD2) which facilitates proteasomal degradation of HIF-1α (McMahon et al., 2006) and IL-1β induces HIF-1α expression through NF-κB and COX-2 (Jung et al., 2003b). Likewise, both environmental hypoxia and intrinsic hypoxia have been found to affect the expression of inflammatory mediators such as chemotaxtants, scavenger receptors, immunomodulatory, adhesion and co-stimulatory molecules, chemokines/cytokine receptors in immune cells (Bosco et al., 2006; Blengio et al., 2013).

Impact of hypoxia on inflammation is primarily driven by HIF-1/2α. HIF-1α and HIF-2α regulate variety of cell signalling molecules involved with inflammatory response and can also directly act as transcription factors for many of them (Taylor et al., 2016). HIFs can regulate multi- variation immune processes like M1/M2 polarization, bactericidal potential of macrophages and neutrophils and antimicrobial peptide production. HIFs also assist in migration and interferon synthesis by dendritic cell (DCs) (Winning and Fandrey, 2016). The crosstalk between HIFs and NF-κB plays important role in hypoxia immune responses. HIF-1α regulates NF-κB signalling by modulating IκB (Inhibitor of NF-κB) (Eltzschig and Carmeliet, 2011; Reyes et al., 2020).

Hypoxic microenvironment can be generated by respiratory viral diseases like bronchiolitis and pneumonia, exacerbations in asthma (Kelly et al., 2010; Yamaya, 2012) and COPD (Frickmann et al., 2012; Wedzicha, 2004). Influenza infection can increase ROS in the lungs leading to stabilization of HIF and can affect immune cells (Chien et al., 2006; Ren et al., 2019; Schlie et al., 2020). Such hypoxic microenvironment can amplify the signalling cascade downstream of TLR2 and TLR6 involving the NF-κB (Kuhlicke et al., 2007). This augments anti- microbial peptide synthesis, phagocytosis, transmigration and adaptive immune response (Eltzschig and Carmeliet, 2011; Kuhlicke et al., 2007).

SARS-CoV causing severe acute lung injury followed by hyper inflammation elicits hypoxia response and augmentation of HIFs. Further, pulmonary dysfunction and fluid accumulation in alveolar spaces can affect gas exchange and aggravate hypoxic microenvironment increasing blood-gas barrier permeability. The crosstalk between inflammation and hypoxic microenvironment is known to modulate the cytokine responses through NF-κB pathway (Jahani et al., 2020). SARS-CoV which shares 79% identity to SARS-CoV-2 may cause accumulation of HIFs due to inhibition of proteasomal degradation and decrease in prolyl hydroxylase activity (Vassilaki and Frakolaki, 2017; Peyssonnaux et al., 2015; Serebrovska et al., 2020).

6. Effect of high-altitude hypobaric hypoxia on severity of viral infections

Hypobaric hypoxia is one of the dominant environmental features of high altitude. Sojourners to mountains therefore develop hypoxia-induced mountain sickness and are often confronted with myriad of health problems. High-altitude hypobaric hypoxia can increase pulmonary hypertension and even result in oedema, therefore leading to poor exchange of gases and hypoxemia (Neupane and Swenson, 2017). Respiratory diseases characterized by pneumonia are a common feature at high altitude amongst the travellers. It has been observed that pulmonary infection can make an individual more susceptible to acute mountain sickness (Basnyat et al., 2001). High altitude has been found to be a risk factor associated with Respiratory syncytial virus (RSV) infection in young children and infant travellers. The risk for RSV-associated hospitalization was highest at elevations above 2500 m (Choudhuri et al., 2006). Both hypoxemia and respiratory infections, primarily the latter, elicit inflammation. In several cases however persistent inflammation can cause irreversible lung damage and the disease outcome can be unfavourable.

It is believed that increased UV-radiation and dry and thin air of high-altitudes may reduce pathogenic transmission and the survivability of virus particles. Epidemiological data suggest decreased severity and mortality in SARS-CoV-2 infection among high altitude population in countries like Nepal and Bhutan. Several studies describe that the (i) decreased half-life of virus due to adverse environmental parameters (ii) decreased ACE2 expression at hypobaric hypoxia environment (iii) improved hypoxia ventilatory response of native highlanders (iv) increased haemoglobin and improved delivery of oxygen (v) increased production of vitamin D and (vi) single nucleotide polymorphism present in ACE2 locus may be lowering the risk and prevalence COVID-19 infection in highlanders (Arias-reyes et al., 2020; Srivistava et al., 2020; Pun et al., 2020). ACE2 expression being reduced by hypoxia however remains controversial as there are articles that report contradictory (Oarhe et al., 2015, Humpl et al., 2015). Also, given environmental hypoxia can increase EPO and VEGFA production, it has been speculated that native highlanders’ physiology may be better equipped to protect against lower ventilatory response and resultant hypoxemia observed in COVID-19. It’s also important to appreciate that although symptoms of hypoxia induced ARDS and COVID-19 induced ARDS may be converging, the pathways involved in the onset of both are unique (Millet et al., 2020).

Another study reports that during the 2009 pandemic of Influenza A (H1N1) virus it was reported in Mexico that high-altitude residence was positively associated with development of pneumonia and adverse outcomes (Perez-Padilla et al., 2013). Later the authors ascribe the phenomenon to increased hypoxemia.

To understand the interplay between hypoxia and inflammation in viral diseases we focused our review on respiratory viruses.

7. Respiratory viruses

Common pathogenic respiratory viruses include rhinovirus (HRV), influenza (IAV), parainfluenza (HPIV) and respiratory syncytial virus (RSV), human metapneumovirus (HMPV) and human coronaviruses. Respiratory viruses attack upper and lower parts of respiratory tract and therefore in severe cases can adversely impact efficient exchange of gases.

7.1. Rhinoviruses

Human Rhinoviruses (HRVs), discovered in 1950s, are common cause of upper respiratory tract infection. It is also responsible for chronic lung diseases like asthma and bronchiolitis in infants, as well as, fatal pneumonia in elderly and immunocompromised adults. More than 100 serotypes of the virus have been found and hence it is difficult to develop a vaccine against it. There are over 62 million annual occurrences of the common cold across the world and out of that HRVs are responsible for more than one half of them. A 7200 bp strand of positive sense RNA makes up the genome of Rhinoviruses. The viral genome encodes for 11 proteins. VP1, VP2, VP3 and VP4 make up viral capsid while rest of the proteins help in viral genesis and propagation. VP1, VP2 and VP3 are responsible for the virus’ antigenic diversity (Jacobs et al., 2013).

The entry mechanism of this virus is based on macropinocytosis via clathrin-dependent or -independent endocytosis (Blau, 2016). Inside the cells of upper respiratory tract, virus starts replicating and its unchecked replication recruits immune cells that release various cytokines. HRV infection of bronchial epithelial cells induce the secretion of inflammatory cytokines and chemokines including IL-1, IL-6, IL-4, IL-5, IL-8, IL-13, GM-CSF, eotaxins, and regulated upon activation, normal T-cell expressed and secreted (RANTES) (Kelly et al., 2010; Southworth...
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Influenza A Virus (IAV) infections are a major cause of severe acute pneumonia worldwide. It often leads to acute lung injury and ARDS. It has a high risk of morbidity and mortality (Potter, 2001). Influenza is known to affect almost 5% of the global population each year, which are nearly 1 billion infections. Every year 3–5 million cases are reported to be severe, having a mortality of 300,000 to 500,000 people (Clayville, 2011). Its genome constitutes of a negative sense RNA. There are 3 types of influenza viruses- A, B and C based on their core proteins. Type A is classified on the basis of its surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA) (Nelson and Holmes, 2007). IAV enters the cells via receptor-mediated endocytosis. Upon endocytosis, the virus navigates to endosomes to release its genome in the host cell (Rumschlag-booms and Rong, 2013).

Proinflammatory cytokines such as TNF-α and IL-6 released upon infection with influenza virus can damage the alveolar-capillary membrane and thus lead to oedema (Bian et al., 2014; Hagau et al., 2010). Resultant poor exchange of gases at the alveolar-capillary membrane ensues into hypoxemia and eventually ARDS (Salihfendic et al., 2015). Influenza virus infections like that of H1N1 and H5N1, HIFs play a major role by increasing the expression of TNF-α and IL-6 and by decreasing the levels of IL-10 (Guo et al., 2017; Zald, 2015). Differential expression study of proteins in mast cells infected with IAV has shown modulation of molecules associated with the HIF-1α pathway. MTOR, a critical regulator of autophagy was seen to be upregulated significantly. (Ren et al., 2019). Interestingly, HIF-1α deficient lung epithelial cells exhibited increased viral replication by reducing glycolysis and enhancing AMPK-ULK1-mediated autophagy (Zhao, 2020). This suggests a major role of HIF-1α in the viral replication, cytokine response and lung inflammation in IAV infections.

Respiratory syncytial virus (RSV) contributes majorly to lower respiratory infections. It is responsible for almost one third cases of the same (Shi et al., 2017). Respiratory syncytial virus affects nearly all children by the age of two years. Hospitalization is reported only up to 2.0% of all infected children. Most of them are affected by lower respiratory tract diseases like bronchiolitis and pneumonia (Paes et al., 2011). RSV has a negative-sense single stranded RNA genome (Rima et al., 2017). Only one serotype of RSV is reported till date with two antigenic groups, A and B. Prevalence of RSV A is known to be more than that of RSV B alongside a marginally higher pathogenicity (Meng et al., 2014).

Entry of RSV in target cells is mediated by protein F and G. These proteins bind to cellular glycosaminoglycans (Hallak et al., 2000). The virus enters the host cell by micropinocytosis followed by activation of the F protein (Krzyzaniak et al., 2013). RSV infections have been correlated with increased levels of the following cytokines and chemokines in lower respiratory tract - IL-4, IL-5, IL-6, IL-10, IL-35 and IL-13. (Fan et al., 2018; Lee et al., 2007; Morichi et al., 2011). Elevated levels of proinflammatory mediators IL-6, IL-8, IFN-γ and MIP-1β are also found in RSV infections (Bennett et al., 2007). MIP-1α, RANTES and MCP-1 are present at higher concentration at low oxygen concentration in RSV infection (Garofalo et al., 2001).

In vitro studies on RSV infections have suggested that HIF-1α is stabilized by increased nitric oxide synthesis (Kilani et al., 2004). HIF-1α activation in RSV infection increases the expression of vascular endothelial growth factor (VEGF), CD73, and cyclo-oxgenase-2 (COX-2) (Haeberle et al., 2008). VEGF can increase vascular permeability and enhance NO production in vivo. This leads to airway mucosal oedema, leading to bronchiolitis and pneumonia in RSV infections (Garofalo et al., 2013). This storm of inflammatory and endothelial factors may lead to severe lung damage and ultimately lead to hypoxemia, which has been found to occur in some cases of RSV infections (Morichi et al., 2011; Chan et al., 2002).

7.4. Bocavirus

In 2005, human bocavirus (HBoV) was first detected in nasopharyngeal aspirates obtained from children with acute respiratory infections in Sweden (Allander et al., 2005). HBoV is the fourth most prevalent viral infection in children hospitalized with respiratory disease after respiratory syncytial virus (RSV), rhino- and adenovirus in Spanish children (Calvo et al., 2008). HBoV contains a single-stranded linear DNA genome of about 5300 bps and belongs to the family Paroviridae. Four species of HBoV have been identified yet, namely HBoV1, HBoV2, HBoV3 and HBoV4, differentiated on the basis of its major structural viral protein 2 (VP2) (Jartti et al., 2012). HBoV has been found in individuals of all ages, although it mainly affects infants aged 6–24 months old with respiratory symptoms (Jartti et al., 2012; Kesebir et al., 2006).

The main clinical features of HBoV-positive patients are respiratory distress and hypoxia (Arnold et al., 2006; Moriyama et al., 2010; Tran et al., 2014). HBoV-positive patients are highly susceptible to pulmonary inflammation and fibrosis and have been found to have a high level of cytokines including EGF, VEGF, GM-CSF, Leptin, TARC (CCL17), IP10, IL-1β, BDNF, FGF-9, TNF-α, TNF-β, Eotaxin-2 (CCL24), IL8, IL-16, GDNF, TIMP-1, RANTES (CCL5), IL-3, and NAP-2 (CXCL7) (Khalfaoui et al., 2016). These high levels of pro-inflammatory cytokines can cause pulmonary damage and initiate fibrosis. Most of the patients suffering from HBoV infection develop fibrotic lungs. Also, hypoxia is a characteristic feature of HBoV-positive patients (Moriyama et al., 2010; Tran et al., 2014).

Although there is no study explaining the relation between inflammatory events and hypoxemia in HBoV infections, we assume high inflammation and fibrosis may be promoting hypoxemia.

7.5. Parainfluenza

The human parainfluenza viruses (HPIVs) also contribute to respiratory diseases such as upper respiratory tract illness (URTt) and lower respiratory tract illness (LRTt), especially in children. HPIVs have 5 serotypes HPIV-1, HPIV-2, HPIV-3, HPIV-4a, and HPIV-4b in 2 different genera Respirovirus (HPIV-1 and HPIV-3) and Rubivirus (HPIV-2 and HPIV-4). The HPIV-1, HPIV-2 and HPIV-3 together make up for 2%–17% of cases of the acute respiratory infection among children up to 5 years in the USA (Jiu et al., 2013). HPIVs are spherical shape viruses and have a single stranded negative sense RNA genome (Moscona, 2005).

Hemagglutinin-neuraminidase (HN) domain of the virus binds to sialic acid–attached receptors on the host cell surface. Then viral fusion protein (F protein) helps in the fusing of the of viral envelope with plasma membrane of the target cell (Plemper et al., 2003). The major organ affected by this virus is lung. HPIVs bind and replicate in the
5

MERS-CoV outbreak was reported in 2012 in the middle-east and manifested as respiratory syndrome as well as renal failure in several patients. This virus primarily affects the lung parenchyma and infects persons. This virus primarily affects the lung parenchyma and infects others S proteins facilitates fusion with and entry into host cell. How ever, it shares less than 90% homology with other viruses in family (Chen et al., 2020). The SARS-CoV S protein has more affinity for ACE2 receptor than SARS-CoV-2 but the former has a furin dependent cleavage site which enables its more efficient entry into cells (Rossi et al., 2020). MERS-CoV also codes for S, E, M, and N proteins and like others S proteins facilitates fusion with and entry into host cell. However, it shares less than 90% homology with other viruses in family (Chen et al., 2020).

8.1. MERS-CoV, middle east respiratory syndrome, or MERS

MERS-CoV outbreak was reported in 2012 in the middle-east and manifested as respiratory syndrome as well as renal failure in several patients. This virus primarily affects the lung parenchyma and infects through dipeptidyl peptidase 4 receptor. This receptor is highly expressed by pneumocytes, endothelia and macrophages. MERS-CoV is endowed with the capacity to evade the immune response (Chen et al., 2020).

This has been especially observed in cases with either poor or fatal outcome. One report suggests that in a patient with fatal outcome IFN-α response wasn’t elicited properly and the cytokine milieu was primarily dominated by IL-10 and CXCL10. Suppression of IFN-α was observed to be due to downmodulated gene expression of RIG-1, MDA-5 and also IRF3. IL-10 and CXCL10 can dampen effective adaptive anti-viral response. The fatal patient also showed augmented expression of IL-23 and IL-17 A in serum and BAL supernatant. These two cytokines are known to be associated with T helper 17 response and tissue destruction (Faure et al., 2014).

Few studies have shown that in severe cases, within 7–10 days, a sharp peak in peripheral count of monocytes and neutrophils take place. This is accompanied by lymphocytopenia. However, patients with good outcome show a slow increase in their lymphocyte count (Min et al., 2016). Another study too has shown that CXCL10 and IL-6 in the sera of MERS patients may be predictors of disease severity and poor outcome. CXCL10 is an inducer of IFN-γ and therefore uncontrolled production of CXCL10 can lead to excessive IFN-γ. Being a chemoattractant, CXCL10 can increase chest infiltrates in the second week following disease onset (Kim et al., 2016).

One of the cardinal features of severe form of the disease is hypoxemia. Severe patients also show either ARDS or pneumonia with prominent chest infiltrates which may be lethal. A section of patients can increase chest infiltrates in the second week following disease onset (Kim et al., 2016).

8.2. Severe acute respiratory syndrome coronavirus (SARS-CoV)

China had first experienced the outbreak of SARS-CoV virus in 2003.
It creates havoc in the lower respiratory tract and the lung parenchyma. Therefore has high fatality rate (B. Chen et al., 2020). In patients with fatal outcome, in a multivariate model it has been associated significantly with thrombocytopenia and hypoxemia (Zou et al., 2004). In fact, one study shows that oxygen desaturation in 54 patients is positively associated with viral load in the serum and also in 154 patients with that of viral load in the nasopharyngeal aspirates (Huang et al., 2004). Another study with 14 participants found that treatment of severe hypoxemia using Nitric oxide resulted in remarkable decrease in pulmonary infiltrates (Chen et al., 2004). It indicated not only Nitric oxide’s beneficial use but the major role hypoxemia plays in development of chest congestion. This may lead to poor clearance of viruses from the lungs leading to enhanced replication and pulmonary damage.

In a China based case study, the patient’s oxygen saturation improved significantly post treatment with corticosteroids (Zhong and Zeng, 2003). Corticosteroids reduce inflammation. Its administration leading to improvement in oxygen saturation hinted that hypoxia observed in patients may also be because of increased requirement of oxygen in the lungs due to aggressive infiltration by immune cells. Also the mediators released by immune cells may lead to vasoconstriction and hyper secretion of mucus. A study shows that cytokines IFN-γ, IL-18, TGF-β, and IL-6 and chemokines IP-10, MCP-1, MIG, and IL-8 are elevated in the sera of patients. Cytokines IL-18, IP-10, MIG, and MCP-1 and chemokine IL-8 were significantly elevated in the group of patients who couldn’t survive. IP-10, MIG, and MCP-1 are chemokines associated with activated T cells while IL-8 is a chemokine associated with neutrophils and therefore the paper postulates that it may be extensive inflammation that causes lungs to collapse in fatal cases of SARS. IL-10 response was found to be very limited and in reciprocal association with IFN-γ. All the cytokines and chemokines had subsided during the convalescent phase (Huang et al., 2005). Another work which performs genomic as well as proteomic analysis shows significantly high amount of IFN-α and IFN-γ in the sera of SARS patients in acute phase. Chemokines CXCL10 and CCL2 and anti-viral genes CIG5 and MXA, which are IFN stimulated, were also high in the sera of patients. During crisis phase however a decline in these chemokines and anti-viral genes were observed in the patients with good outcome. But in cases with hypoxemia and fatality these chemokines did not subside with time. Atypical antiviral response through IFNAR1, IFNGR1, and the costimulatory molecule CD58 was observed to be persistent in these patients. These patients also showed very poor expression of HLA and Ig genes. This was consistent with the fact that anti-SARS-CoV spike protein antibody was rarely observed in patients with poor outcome. This paper therefore suggests that hyper innate response in severe patients is associated with poor development of adaptive immune response resulting into poor or fatal outcome (Cameron et al., 2007). Another paper however reports no significant increase in IFN-γ during acute phase. This paper reports that SARS patients have significantly higher IL-6:IL-10 ratio than community acquired pneumonia patients (Chien et al., 2006).

8.3. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

It is in December 2019 that the first infection by SARS-CoV-2 was reported in Wuhan, China. Since then it has spread across the world to give rise to a pandemic with fatal consequences in a certain section of patients. The fatality rates may be an over estimation given the poor recording of asymptomatic cases and varying testing rates across the world. In fact, the low mortality rate may be the cause why the infection has spread across the world. Although mortality rates may be lower, severe COVID-19 often leaves the patient with long term problems like pulmonary embolism, neuropsychiatric disorders and cardiac complications. These long term effects may be both due to the upheaval of non-specific inflammation as well as side effects of the present medications being used.

8.3.1. Phases of infection

The infection of the airway epithelium is reported to happen through the human ACE2 receptor by the RBD domain on the virus (Shang et al., 2020). SARS-CoV-2 has three phases of infection-nasopharynx cells, upper respiratory tract and then the parenchymal-alveolar region. The disease remains either asymptomatic or mildly symptomatic till the second phase and usually phases out. However it is reported that 20% of patients proceed to the third phase which gives rise to a severe manifestation of the infection (Mason, 2020). The mean age of severe disease across the world is 75 years (Wu and McGoogan, 2020). Few reports suggest lower expression of ACE2 in children and adolescents as compared to the older adults and therefore lower rates of infections in the former age group (Bunyavanchich et al., 2020).

The innate response primarily begins in the second phase of the

### Table 3

| Parameters                  | Asymptomatic | Moderate | Severe | References |
|-----------------------------|--------------|----------|--------|------------|
| Monocyte count              | NS           | NS       | NS     | Li et al. (2020), Hadjadj et al. (2020), Jiang et al. (2020) |
| Neutrophil count            | NS           | NS       | NS     | Jiang et al. (2020), ALJishi et al., 2021, Hadjadj et al. (2020) |
| Neutrophil percentage       | Low          | High     | Very high | Zheng et al. (2020), Lucas et al. (2020), Schulte-Schrepping et al. (2020) |
| Lymphocyte percentage       | High         | Low      | Very low | Zheng et al. (2020), Lucas et al. (2020) |
| Lymphocyte count            | High/Normal  | Low      | Very low | Han et al. (2020), Jiang et al. (2020), Zheng et al. (2020), Hadjadj et al. (2020), Sharma et al. (2020) |
| CRP                         | Low          | High     | Higher | Ma et al. (2020), Li et al. (2020) |
| IL-6                        | Low          | High     | Very high | Jiang et al. (2020), Zheng et al. (2020), ALJishi et al., 2021, Zeng et al., 2020 |
| TNF-α                       | N.S          | N.S      | N.S    | Lucas et al. (2020) |
| IL-18                       | Low          | High     | Very high | Lucas et al. (2020), Chi et al. (2020) |
| IFN-α                       | High         | High     | N.S    | Lucas et al. (2020), Trouillet-Assant et al. (2020) |
| IFN-γ                       | Low          | High     | Higher | Lucas et al. (2020), Villalba et al. (2020) |
| Abnormalities in chest CT   | Absent       | Low      | High   | Zheng et al. (2020), Yu et al. (2020) |
| Bilateral pneumonia         | Absent       | Low      | High   | Li et al. (2020), Ma et al. (2020) |
| Dyspnea                     | Absent       | Low      | High   | Jiang et al. (2020), Ding et al. (2020) |
| Hypoxia                     | Absent       | Low      | High   | Zheng et al. (2020) |

NS ~ non-significant.
infection. It has been observed that CXCL10 expression significantly enhances during this phase and may be used as a phase indicator of the disease (Tang et al., 2005). The first two phases usually comprise of 5–7 days. If the infection does not get cleared at this phase, it proceeds to infect the alveolar cells of the parenchyma and pleural region as shown by High Resolution-CT Scan of the lungs (Wu et al., 2020; Zhang et al., 2020). A case report studying the lung biopsy sample from a COVID-19 patient clearly showed infiltration by monocytes and lymphocytes, pulmonary oedema and squamation of the alveolar cells. This indicated development of ARDS (Xu et al., 2020). It may be presumed that the developments observed in the HR-CT studies may be eventually giving rise to the ARDS observed in severe patients of COVID-19.

The three most baffling aspects of this infection has been its ability to develop cytokine storm, presence of silent hypoxia and a high number of asymptomatic patients. We have hereafter discussed the salient features of incidents of cytokine storm and silent hypoxia. In Table 3, we have listed the presently known differences in immune parameters between mild and severely symptomatic and asymptomatic patients. The table is a comparative presentation based on data reported till now in order to enhance our comprehension of possible differences in immune response in COVID-19 patients thus resulting in a broad range of degree of symptoms.

8.3.2. COVID-19 and cytokine storm

Cytokine storm (CS) has been noted widely in severe and critical patients of COVID-19. Cytokine storm is an umbrella term that refers to uncontrolled secretion of cytokines and chemokines due to persistent activation of immune cells and resulting in increased infiltration of the interstitial tissues of the lungs with neutrophils and lymphocytes primarily. In the periphery is therefore observed lymphocytopenia (Chen et al., 2020). IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP-1α, hepatocyte growth factor (HGF), TNF-α, and vascular endothelial growth factor (VEGF) (Huang et al., 2020; Zhang et al., 2004) are the cytokines that have been observed to be increased in the sera of hospitalized patients. However, mortality has been positively associated with serum IL-6 level. The severe and critical patients show significantly higher level of IL-6 in their sera (Gao et al., 2020). Also, C-reactive protein and IL-6 have emerged to be critical predictors of mechanical ventilation (Shimizu, 2019). IL-1, IL-6, IL-18, IFN-γ, and TNF-α cytokines have been identified as the primary orchestrators of cytokine storm (Hojyo et al., 2020). IL-6 is an inducer of STAT3, therefore a review postulates that STAT3 activation may be dominantly associated with development of CS (Xiong et al., 2020). A study with critically ill patients show significant correlation between serum load of viral RNA and IL-6 (Chen et al., 2020). IL-18 and IL-33 are known mediators of systemic inflammation and are released by damaged tissue. One transcriptomics study has shown significant upregulation of IL-33 and IL18 in BALF and PBMCs of patients respectively (Xiong et al., 2020). One study has shown that elevation in serum level of IL-33 is associated with poor outcome in patients the age of 70 (Burke et al., 2020) and another has associated elevated serum IL-18 poor outcome in severe patients (Satsui et al., 2020). It is being presumed that this hyperinflammation may lead to activation induced cell death (AICD) in T cells due to hyperactivation by the circulating IL-10 and IL-2R and therefore resulting in lymphopenia (Jafarzadeh et al., 2020).

8.3.3. Silent hypoxia and its causes

One of the striking features of several SARS-CoV-2 patients is the quite presence of hypoxemia. Hypoxemia refers to a percentage of blood oxygen saturation level lower than that required for normal functioning of the body (less than 92%). This usually leads to dyspnoea (shortness of breath) and dizziness and several other complications. However, in the case of COVID-19, it has been observed that although the patient is hypoxemic, the patient either displays no apparent symptoms of the same or reports only mild shortness of breath. Thus it is being referred to as silent hypoxia (Dhont et al., 2020). The alluring question till now is that how does this silent hypoxia develop in the patients. No concrete evidence has established the exact causation; few recent articles attempt to underline possible reasons. One paper suggests that dyspnoea as a result of hypoxia is due to increased ventilation. Increase in ventilation occurs due to signals transduced by the medulla oblongata. Silent hypoxia has been primarily observed in old-age group patients and patients with diabetic condition. Both aging and diabetes can impair ventilation. Therefore this study proposes that lack of dyspnoea may be because of intrinsic poor ventilation (Tobin et al., 2020). Another work postulates that it is SARS-COV-2 mediated neuronal damage that may be resulting in non-dyspnoea hypoxia. This neuronal damage is caused either directly by the virus by infecting the cells of the limbic system or cytokine storm adversely impacting the corticobulbar system. The direct infection may be due to ACE2 receptor being present on cells of the limbic system. These are the areas of the CNS which are responsible for regulation of dyspnoea (Nouri-vaskeh et al., 2020). Another paper using mathematical modelling based on data obtained through CT-scans. In case of lung injury, the arteries undergo vasoconstriction. Thus, perfusion of blood is only through regions which are not injured. This redirection is usually captured in CT-scans. In most COVID-19 patient CT-Scans it was observed that blood continued to perfuse in areas where there is lung injury. The other reason could be formation of small blood clots along the lining of the blood vessel as a result of endothelial dysfunction. These clots would restrict the flow of blood and eventual exchange of gases. Inflammation of the lower respiratory tract may also lead to lower air to blood ratio (Hermann et al., 2020) Two papers seem to suggest formation and presence of these clots may be associated with pathogenesis of ARDS in severe patients (Cicieri et al., 2020; Xu et al., 2020). Another in silico report suggests that SARS-CoV-2 RNA may have the ability to translocate to host cell’s mitochondria (Wu and Chang, 2020). It is reported that healthy mitochondria are a prerequisite for proper exchanges of gases in the lungs (Cloonan and Choi, 2016; Suliman et al., 2017). So, it may be examined if localized viral RNA may cause mitochondrial dysfunction in the host cell and therefore reduce ventilation and cause hypoxemia. Also, it may be possible that mitochondrial dysfunction in the cells of medulla oblongata impairs its ability to increase ventilation in response and therefore letting the hypoxemia to be silent.

8.3.4. Hypoxia and inflammation COVID-19

One of the mechanisms by which SARS-CoV-2 infects cells is by binding to the receptor ACE2. ACE2 is a receptor whose expression has now been shown to be downregulated by HIF1α. HIF1α is stabilized by hypoxia as well as inactivation of PHD2. It has been shown that RSV and H1N1 can inactivate PHD2 but such an observation in case of SARS-CoV-2 remains elusive. SARS-CoV-2 infection at the LRT results in poor exchange of gases at the alveoli and therefore there is development of hypoxemia. But the infection itself leads to HIF1α accumulation in lung epithelia and alveolar cells resulting in release of vascular permeability enhancer, VEGFA. HIF1α is by itself a transcription factor for several pro-inflammatory cytokines which can activate the pulmonary leukocytes. HIF1α mediated release of chemokines in combination with the above two factors lead to rapid infiltration of the lungs by monocytes, dendritic cells and neutrophils. This infiltration in itself results in occlusion of not only airways but capillaries too. This probably facilitates development of a hypoxic environment in the lungs. Accumulation of a large number of immune cells and oxygen paucity due to occlusion, together forces the cells to shift to anaerobic glycolysis. Anaerobic glycolysis may help in replication of viruses. So inflammation induced hypoxia and then hypoxia induced inflammation may be responsible for wreathing the havoc of systemic cytokine storm and eventual damage of the lungs. Our knowledge till now remains more speculative rather than substantiated by experimental evidence (Serebrovskaya et al., 2020; Østergaard, 2021; Fernandes et al., 2020).
8.3.5. COVID-19 and ARDS and pulmonary fibrosis

The severe and critical nature of the disease is a result of acute respiratory distress syndrome (ARDS) in the lungs (Acosta and Singer, 2020; Fan et al., 2020). Patients, who survive ARDS, eventually live with lung fibrosis of varying degrees (George et al., 2020; Ojo et al., 2020). This is because as the body attempts to recover from ARDS, fibroblasts proliferate rapidly and lead to massive amount of extracellular matrix deposition. This is the causative agent of fibrotic lungs (Burnham et al., 2014; Cabrera-Benitez et al., 2014). In the previous section we have discussed that IL-33 has been significantly associated with disease severity and poor outcome. Interestingly, IHC of lung sections from patients of Idiopathic pulmonary fibrosis show increased expression of IL-33 (Luzina et al., 2012). In fact in various fibrotic diseases and their animal models IL-33/ST2 pathway has proven to be associated with development of fibrosis (Gao et al., 2015). Another molecule HMGB1, a molecule known to be associated with ARDS, can also transcribe VEGF which increases vascular permeability and therefore the immune cells can enter the airway. Neutrophil degranulation here leads to increased mucous secretion by the Goblet cells. This mucous may be utilised by some viruses to support their replication through increased glycosylation. This inflammatory upheaval can not only enable virus clearance but also create systemic inflammation and also may damage portions of the lung due to tissue destruction and lead to ARDS. Recovery from such tissue damage may lead to fibrosis and render that portion of the lung incapable of efficient gas exchange. (The image has been created using tools on Biorender)

8.4. Other coronaviruses

The other common strains of coronavirus known to impact humans are 229 E, NL63, OC43 and HKU1 (Su et al., 2016). Infection by any of these strains tends to show similar symptoms of coughing, fever, nasal discharge and headache. HCoV 229 E is a strain of coronavirus which was isolated for the first time from medical students with common cold. It’s primarily causes upper respiratory tract infection and rarely infects the lower (Hamre et al., 1967). NL63 was detected for the first time in aspirate collected from the nasopharynx area of a 7 month old patient (Hoek et al., 2006). The virus causes both upper and lower respiratory tract infection. In upper respiratory tract infection, a condition called Laryngotracheobronchitis or Croup is often observed. It presents with inflamed larynx and trachea. NL63 can cause Bronchiolitis in case of lower respiratory tract infection. It is an inflammation in the membranes which line the tiny bronchioles (Abdul-Rasool and Fielding, 2010). OC43 too has been associated with development of common cold. It primarily affects the lower respiratory tract and Bronchiolitis can be observed (Su et al., 2016; Hoek et al., 2006; Chang et al., 2020). HKU1 was detected for the first time in a 71 year old man with pneumonia. It can cause both lower and upper respiratory disorder (Kanwar et al., 2017). One study shows that individuals with clinical history of
respiratory complications may be more susceptible to HKU1 infection (Esper et al., 2006).

9. Therapeutic intervention

Vaccine is the most impactful preventive strategy in case of viral diseases. However, given the rapid and ever evolving nature of viruses, it’s important for us to have novel therapeutics at place. Among all respiratory viral diseases, a common node is hypoxia and hypoxia responsive molecules such as HIF-1α and HIF-2α, which are associated with the development of inflammation in the airways and lung parenchyma. Literature suggests testing HIF-1α inhibitors like RNA antagonist EZN-2968, which are in clinical trial for cancer treatment, to reduce disease morbidity in respiratory viral infections (Gan and Ooi, 2020). Also, several approved drugs in use like metformin, atorvastatin etc. are known to indirectly abrogate HIF-1α stability and signalling. Some works have suggested repurposing them to manage inflammation in the lung (Liu et al., 2020). A recent work suggests making PHD2 inhibitors a part of COVID-19 treatment regimen to increase erythropoiesis and reduce ferroptosis (Poleznikov et al., 2021). Most of the complications suggested to be resolved by PHD2 inhibitors are impacts of excess inflammation at initial stage. We suggest that if PHD2 activity can be augmented at the initial stage using small molecules then HIF-1α mediated inflammation and viral replication may be partially harnessed. Also, proteases released by cells like Neutrophils can cause mucus hyper-secretion in the airway leading to obstruction to smooth airflow. Protease inhibitors may be employed to limit mucus secretion. Antioxidants too can become a major part of treatment regimen as several viruses generate ROS and NO to stabilise HIF-1α.

10. Conclusion

Respiratory viruses cause wide spectrum of inflammation in the lungs. In general, inflammatory response peaks during the acute phase of infection and decreases during convalescent phase but consequences such as systemic inflammation often persist. In some cases, during acute phase patients display excessive level of cytokines in circulation, referred to as cytokine storm. SARS-CoV has been reported to mediate NLRP3 inflammasome activation and assembly along with mitochondrial ROS and K+ efflux. This leads to elevation of IL-1 family of cytokines. In severe patients of RSV, MERS and SARS, cytokine storm may impair ventilatory response and reduce arterial oxygen partial pressure, known as hypoxemia. Both, inflammation induced hypoxic microenvironment and hypoxemia can initiate parenchymal damage and also support virus propagation. It leads to stabilization of HIFs which can further aggravate inflammatory response. We have presented a generic idea in the schematic Fig. 1.

In case of COVID-19, silent hypoxia is a salient feature of severe and fatal cases. Silent hypoxia is only observed in cases where the infection spreads to lower respiratory tract (LTR) which is accompanied by cytokine storm in severe COVID-19 patients. Most of the patients with SARS-CoV-2 who require hospitalization and intensive care develop acute respiratory distress syndrome (ARDS), an effect of prolonged hypoxemia and inflammation. Although this review discusses about the interplay between inflammation and hypoxia in disease pathogenesis of respiratory viral diseases, several questions remain inconclusive—whether the hypoxia responsive factors including HIFs have a role to play in this hyper inflammation.

Author contributions
SB, SA and NMS provided conceptual inputs for various parts of the article and wrote. SB edited the article. PG conceptualized whole articles, wrote and edited. All authors read and approved the final article.

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Declaration of competing interest
The authors declare no competing interests.

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