REVIEW

SARS-CoV-2 Infection: Host Response, Immunity, and Therapeutic Targets

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Abstract—Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has resulted in a global pandemic with severe socioeconomic effects. Immunopathogenesis of COVID-19 leads to acute respiratory distress syndrome (ARDS) and organ failure. Binding of SARS-CoV-2 spike protein to human angiotensin-converting enzyme 2 (hACE2) on bronchiolar and alveolar epithelial cells triggers host inflammatory pathways that lead to pathophysiological changes. Proinflammatory cytokines and type I interferon (IFN) signaling in alveolar epithelial cells counter barrier disruption, modulate host innate immune response to induce chemotaxis, and initiate the resolution of inflammation. Here, we discuss experimental models to study SARS-CoV-2 infection, molecular pathways involved in SARS-CoV-2-induced inflammation, and viral hijacking of anti-inflammatory pathways, such as delayed type-I IFN response. Mechanisms of alveolar adaptation to hypoxia, adenosinergic signaling, and regulatory microRNAs are discussed as potential therapeutic targets for COVID-19.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) [1] is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] in humans. Since the start of the pandemic in 2020, COVID-19 has caused nearly 5 million deaths worldwide, with hundreds of millions of people testing positive for SARS-CoV-2 (https://covid19.who.int) accessed on 10/29/2021. Efficient human-to-human transmission facilitated global spread following initial failures of containment [2–4], and after more than a year of widely variable worldwide attempts to mitigate disease progression, vaccination has offered hope of limiting disease in many parts of the world [5–7]. However,

resistance towards vaccination efforts in combination with strains that are more easily transmitted has led to increasing rates of hospitalization and mortality during the pandemic. COVID-19 is usually a self-resolving disease and the virus burden can peak as early as day 3 and is usually cleared in one-to-two weeks in healthy individuals [8, 9]. While the symptoms of COVID-19 are mild in the majority of the infected children and young adult population [10], severe disease happens in approximately 13% of the population with over 2% mortality [11]. Serious underlying conditions including immunocompromised individuals, obesity, chronic lung diseases, diabetes, organ transplant, and cardiovascular comorbidities, as well as male sex and older age, are identified as risk factors in increased mortality rates in adults [12–17]. Such patient populations tend to develop more critical complications including ARDS, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure [12, 18–21]. Importantly, liver disease and cirrhosis seem to also contribute to case fatality rates and liver injury is seen in up to 60% of clinical cases [22–24]. Patients with mild symptoms can often recover at home. Hospitalized patients who require supplemental oxygen are recommended remdesivir, dexamethasone, or monoclonal antibodies such as baricitinib or tocilizumab. However, there is currently no cure for COVID-19. SARS-CoV-2 infection not only causes multiple organ involvement in the acute phase of infection, but may also result in a high incidence of post-acute sequelae of COVID (PASC) [25–27]. Approximately, 10–30% of COVID-19 survivors experiences effects beyond 4 weeks of acute onset. The most frequent symptoms are fatigue, dyspnea, anxiety and depression. There are also often detected abnormalities in the renal, cardiovascular, and coagulation systems [26]. Mechanistic insight of the pathogenesis of PASC is needed to improve clinical outcomes.

Coronavirus outbreaks are not novel phenomena, as demonstrated by the severe acute respiratory syndrome epidemic in 2003 (SARS-CoV) and the Middle East respiratory syndrome outbreak in 2012 (MERS-CoV) [28]. Based on characterizations of prior CoVs and rapid worldwide investigations into SARS-CoV-2 [29–31], it was quickly recognized that human angiotensin-converting enzyme 2 (hACE2) is the principal receptor for SARS-CoV-2 spike protein. Among the wide distribution of hACE2-expressing tissues, hACE2 is notably present on the luminal surfaces of respiratory epithelial cells, including type 2 pneumocytes and ciliated bronchial epithelial cells [32]. Engagement of viral spike with hACE2 at these cellular interfaces facilitates viral entry and initiates a cascade of immunological responses that may ultimately result in acute lung injury combined with hypoxemic respiratory failure [33]. Contributing to the challenge of responding to SARS-CoV-2, thousands of viral mutations have already been described, including many spike point mutations (e.g., N501Y, A570D, D614G, P681R, T716I, S982A, and D1118H) and amino acid deletions (e.g., S Δ69–70 and S Δ144) [34–36]. According to the World Health Organization (WHO), four "Variants of Concern (VOC)" (Alpha to Delta) have been identified with a trend in increased transmissibility and antigenicity [36–38]. First identified in India in October 2020, Delta variant has a more than 40% increase in transmission and since spread to over 110 countries. Sequencing and competition studies suggested that the spike is critical for viral transmission. The accumulated mutation P681R at the furin cleavage site of the spike has been proved to significantly increase the viral replication fitness of the Delta variant [39]. The recently emerged "Delta Plus" variant (B. 1.617.2.1 or AY.1) also contains K417N mutation on the RBD of spike. The Omicron variant, causing a recent case surge, is even more infectious than original Wuhan strain of SARS-CoV-2 virus or known intervening variants. The Omicron variant causes attenuated disease in small animal models of SARS-CoV-2 infection [40, 41]. In this review, we will discuss the pathophysiology and experimental models of COVID-19, and highlight potential clinical interventions to prevent and treat COVID-19.

SARS-COV-2 INFECTION AND HOST RESPONSES

Viral Structure and Host-Cell Interactions

SARS-CoV-2, a betacoronavirus, is a member of the *coronaviridea* family, along with other human disease-causing coronaviruses including SARS-CoV and MERS [42]. SARS-CoV-2 is enveloped with a single positive-strand RNA genome contained in a capsid (Fig. 1A). Each SARS-CoV-2 particle contains four main structural proteins: spike, membrane, envelope, and nucleocapsid [43]. The spike protein is heavily glycosylated and mediates anchoring to ACE2, and, together with transmembrane serine protease 2 (TMPRSS2), facilitates viral entry [44, 45]. The viral membrane protein helps in virion assembly and the nucleocapsid protein promotes assembly of the nucleocapsid in association with viral genomic RNA
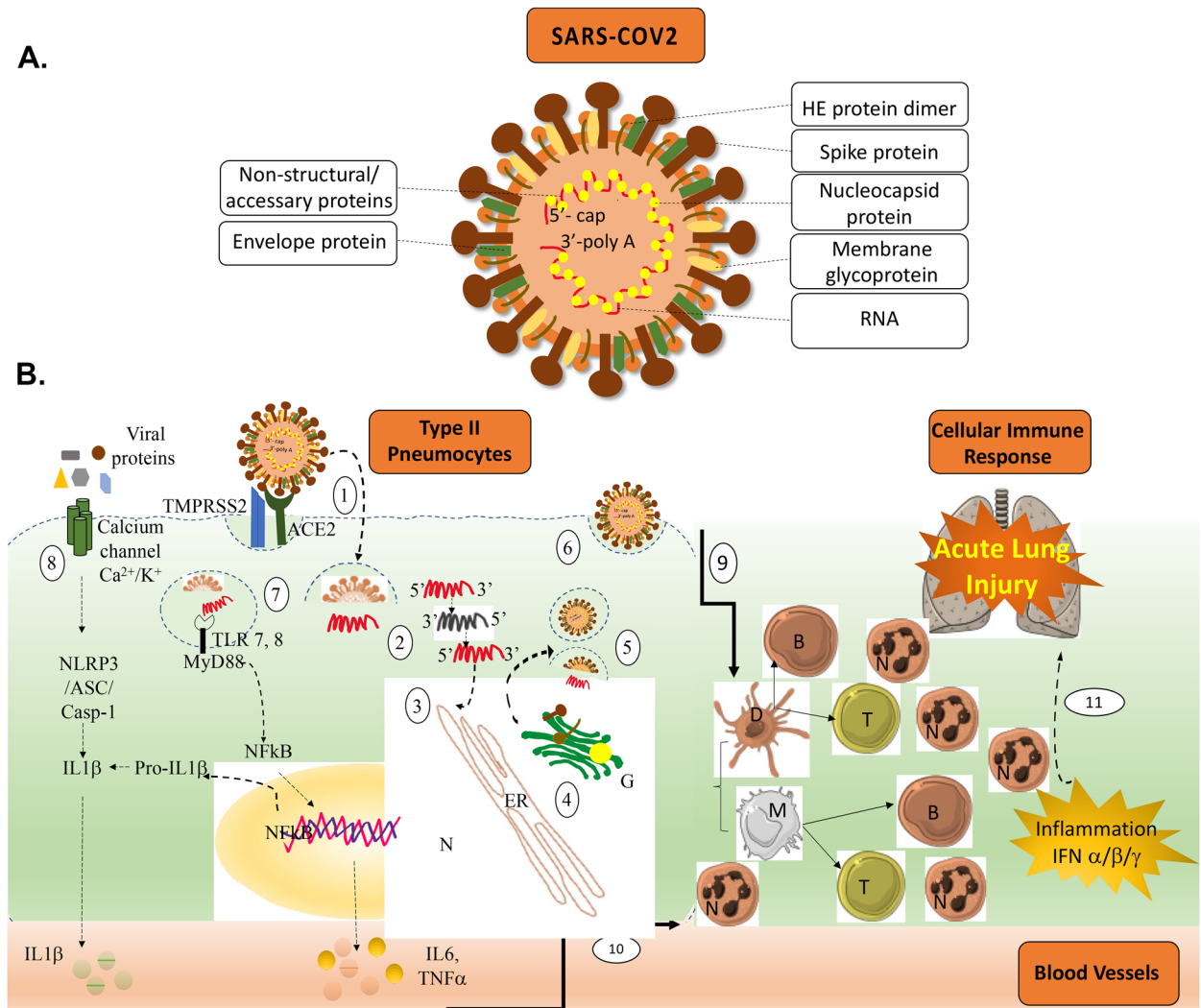
Fig. 1 Structure and Infectivity of SARS-CoV-2 infection and acute lung injury. **A** Schematic structure of SARS-CoV-2 virus is a positive single-stranded RNA virus. Nucleic acid is encapsulated with viral nucleocapsid protein. The outer structure comprises four proteins, namely, envelope protein, hemagglutinin protein dimer, spike protein, and membrane-associated glycoprotein. The accessory proteins or non-structural proteins are encoded by the viral genome to assist infectivity and perpetuation. **B** Cascade of events in SARS-CoV-2 binding and replication and host response. (1) Viral spike binds to ACE2 and entry is assisted by cleavage by TMPRSS2 and fusion of the virus particle. (2) Release of viral genome and replication by viral RNA polymerase, upon which host antiviral/ ds-RNA sensing RIG-I pathway is activated (not shown) to produce interferons. (3) Translation of viral proteins, both structural and non-structural using host rough endoplasmic reticulum. (4) Posttranslational modifications and assembly of structural proteins. (5) Packaging and development of new virions. (6) Exocytosis new virions and infection of new cells. (7) Vesicular internalization is the second mode of viral entry initiating host inflammatory response and chemotaxis via TLR 7,8/MyD88/NFkB pathway. (8) SARS-CoV-2 accessory proteins trigger NLRP3/ASC/Casp-1/IL-1b-dependent pyroptosis. (9) Viral infection and antigen presentation by dendritic cells and macrophages leading to the elicitation of anti-viral response by B and T lymphocytes. (10) Dysregulated inflammatory response and extravasation of neutrophils and cytokine storm results in acute lung injury.

[46]. Intracellular SARS-CoV-2 infection is initiated by the binding of viral spike protein to cell surface ACE2 on alveolar epithelial cells, which results in alveolar inflammation and the release of chemokines and cytokines [33,

47, 48]. Furin-like protease is required for the preactivation of spike cleavage to facilitate quick entry into the cells [49–51]. Upon entry, pathogen-associated molecular patterns (PAMPs) initiate Toll-like receptor signal

transduction, including single-stranded RNA (ssRNA) fragments from the SARS-CoV-2 genome directly activating endosomal TLR7/8 and NFκB transcriptional activation of proinflammatory cytokine production and release follows [52–54]. Furthermore, signal transduction through dsRNA-sensing receptors RIG-1/MDA5 stimulates IFN response via IFN regulatory factor 3/7 (IRF3/7) resulting in type I IFN and chemokine production [53, 55, 56]. The accessory viral proteins along with the spike protein consequently develop calcium/potassium ion channels (unlike the SARS-CoV which develops NA$^+$/K$^+$ channels) and trigger NLRP3 inflammasome pathway thereby leading to IL-1β-dependent pyroptosis, a form of cell death induced by inflammation [57]. Alveolar epithelial pyroptosis further releases danger-associated molecular patterns (DAMPs) in the interstitial space that bind to the DAMP-TLRs, TLR2 and TLR4, on the microvascular endothelial cells thereby activating the production and secretion of proinflammatory cytokines, type-I IFNs and chemokines [58]. Proinflammatory cytokines, including TNFα, IL6, and type I IFNs mediate chemotaxis and/or immune cell dysfunction resulting in ARDS and in tissue damage (Fig. 1B; left panel) [59, 60]. Overactivated immune responses, in turn, result in further tissue damage and organ dysfunction.

SARS-CoV-2-Associated Immunopathogenesis

SARS-CoV-2 infection-driven-immune responses include innate immune sensing, innate immune responses, and adaptive immunity (Fig. 1). Currently, the understanding of SARS-CoV-2 immunopathogenesis relies heavily on human studies and previous knowledge of other coronaviruses, including SARS-CoV and MERS [61]. Innate immune sensing of SARS-CoV-2 is mediated by the recognition of viral RNA by pattern recognition receptors (PRRs) which trigger the release of cytokines and chemokines. An early and sufficient release of cytokines such as IFNs is crucial for the successful control of viral replication and host survival [62]. Many coronaviruses develop strategies to escape innate immune sensing by avoiding PRR activation and by interfering with downstream IFN responses [61]. Recent study indicated that the Alpha variant of SARS-CoV-2 suppresses innate immune responses more efficiently compared to earlier lineages [63]. Mechanistically, increased protein level of Orf9b from the alpha variant interacts with TOM70 and inhibits innate immune responses by dampening RNA sensing in airway epithelial cells [63].

The infected epithelial cells initiate a robust type-I and III IFN (IFN λ binds to IFNLR) response and release inflammatory cytokines including IL-6 and IL-1β to recruit and activate granulocytes, DCs, and macrophages to the lung, driving the immunopathogenesis of SARS-CoV-2 (Fig. 1B; right panel) [64, 65]. Furthermore, increased levels of hyaluronan, which can be elicited by TNF-α and IL6 have been detected in patients with COVID-19 ARDS [66, 67]. Besides the direct stimulation of myeloid cells by infected alveolar epithelial cells, several recent studies suggested that SARS-CoV-2 stimulates monocytes from peripheral blood to elicit inflammatory responses by the release of TNF-α, IL-1β and IL-6 [68, 69], while there is a lack of productive viral replication in these cells. In patients with severe COVID-19, single cell RNA sequencing analysis of bronchoalveolar lavage fluid uncovered abundant proinflammatory monocyte-derived macrophages [70]. In addition, a recent single cell RNA sequencing analysis of the bronchial alveolar lavage fluid from ferrets infected with SARS-CoV-2 identified many subpopulations of macrophages at 2 days post-infection. Additional studies are crucial to illustrate how monocytes functionally contribute to viral clearance and late-stage hyperinflammation [71]. RNA velocity analysis indicated complex kinetics in both M1 and M2 macrophages originated from monocyte-derived macrophages [71], indicating the complex nature of the macrophage responses.

Pulmonary innate lymphoid cells, including natural killer (NK) cells, play important roles in controlling viral infection through type-I IFN (IFNα/β)-mediated IFN γ production (in addition to IL-12 and IL-18) to facilitate helper T cell responses [72, 73]. Several studies have demonstrated a decreased NK cell population in the peripheral blood of COVID-19 patients [74, 75]; however, it is still unclear whether it is the result of NK cell recruitment to the pulmonary microenvironment. Functionally, NK cells in the peripheral blood from COVID-19-infected individuals showed less activated status with potential impairment in cytotoxicity and chemokine/cytokine production [76]. So far, there is no evidence suggesting that SARS-CoV-2 directly infects NK cells. Thus, the aberrant activation status could be partially explained by the increased expression of inhibitory or immune checkpoint molecules such as LAG3, TIM3, and NKG2A in NK cells from COVID-19 patients [76]. Other groups of innate lymphoid cells such as ILC1/2/3 are less studied in SARS-CoV-2 infection. However, based on their important role in promoting the rapid innate immune response to

pathogens, more attention should be given to these cells in the immunopathogenesis of SARS-CoV-2 infection.

Adaptive immunity plays an instrumental role in the control and immunopathogenesis of SARS-CoV-2. Lymphopenia is commonly observed in blood from COVID-19 patients and the degree of lymphopenia is correlated with the severity of the disease [61]. Although the cause of COVID-19 lymphopenia is currently unknown, it was speculated that recruitment of lymphocytes to the infected lung might be a contributing factor [70]. SARS-CoV-2-reactive CD4 and CD8 T cells have been identified in bronchial alveolar lavage fluid and in peripheral blood from COVID-19 patients [70, 77, 78]. In patients with severe COVID-19, the population of regulatory T cells and γδ T cells are decreased [77, 79, 80], suggesting the lack of sufficient immune regulation and viral defense. Similarly, peripheral CD8 T cells from severe COVID-19 patients have reduced cytotoxicity marked by lower expression of CD107a and Granzyme B [74]. Of note, the phenotype and function of CD8 T cells in infected lungs are unlike those observed in peripheral blood as bronchial alveolar lavage (BAL) CD8 T cells expressed higher levels of cytotoxic genes [70]. Thus, future efforts are needed to address the functional relevance and mechanism of the discrepancy. Besides T cells, B cells are important for the production of neutralizing antibodies to defend against viral infections. Indeed, SARS-CoV-2-specific antibodies, as well as plasma cells and memory B cells, have been detected in the majority of COVID-19 patients although the correlation of antibody titers with disease severity is inconclusive [81–83]. Due to its recent emergence, it is essentially unknown how long-lasting the B cell immunity against SARS-CoV-2 is in preventing viral reinfection. However, knowledge from the SARS-CoV-1 and MER-CoV suggested that at least 2 to 3 years are the typical time frame for protection [84, 85]. However, with the emergence of multiple variants of the SARS-CoV-2 viruses, it is unlikely that the neutralizing antibodies will prevent reinfection as effectively did the previous CoVs.

LABORATORY APPROACHES TO STUDY SARS-COV-2 PATHOGENESIS AND HOST RESPONSES

To better understand the pathogenesis of COVID-19, it is crucial to develop experimental animal models to help delineate stepwise mechanisms involved in the pathogenesis of ARDS and multiple organ failure in COVID-19 [86, 87]. Figure 2 illustrates a brief account of laboratory animal models in the establishment of SARS-CoV-2 infections and COVID-19 [88–90].

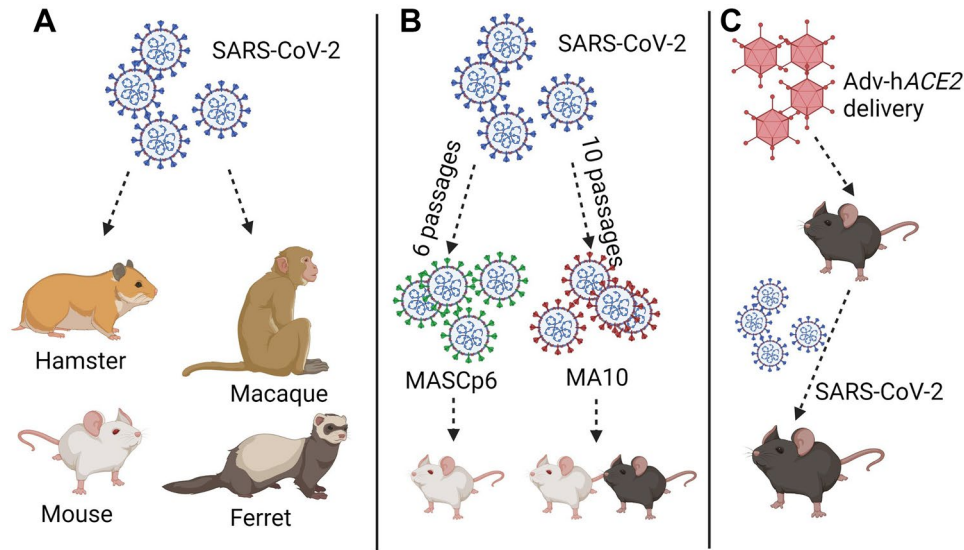## Ferret Model of SARS-CoV-2 Infection

Administration of SARS-COV-2 Wuhan strain SARS-CoV-2 strain BetaCoV/Wuhan/IVDC-HB-01/2019 (CTan-H), or SARS-CoV-2 strain BetaCoV/Wuhan/IVDC-HB-envF13-20/2020 (F13-E), lead to efficient viral replication in ferrets in the nasal turbinates, tonsils, and the soft palates up to day 10 post-inoculation, with 20% mortality by day 10 in CTan-H- and day 11 in F13-E-infected ferrets [88], presumably due to the increase binding affinity of ferret ACE2 to SARS-CoV-2 [91]. A shift in the host response with an increased ratio of production of proinflammatory CCL2, CCL8, and CXCL9 to diminished IFNβ and IFN λ production was observed in SARS-CoV-2-infected ferrets' nasal washes [90]. These phenotypes were consistent with cytokine profiles in serum samples from COVID-19 patients. However, the viral replication is mostly restricted in the upper airway compared to human COVID-19, which is heavily involved in the lung.

Hamster Model of SARS-CoV-2 Infection

Using golden hamster models for human SARS-CoV-2, studies have shown that these animals have increased viral burden in the nasal mucosa and bronchial epithelial cells, associated with lung pathologic changes within day 2 to 5, pneumocyte hyperplasia post-day 7, and regional consolidation and multilobar glass opacity by day 8 followed by viral clearance [92, 93]. However, the hamster model only represents mild-moderate COVID-19, as no mortality is observed in the infected animals.

Nonhuman Primate Model of SARS-CoV-2 Infection

Non-human primates have also been explored in preclinical studies of SARS-CoV-2 infection. Several studies reveal that infection of non-human primates including cynomolgus macaques [94], rhesus macaques, and baboons resemble mild to moderate

Fig. 2 Experimental strategies to study SARS-CoV-2 infection and COVID-19-like disease *in vivo*. **A** Non-human primates, ferrets, golden hamsters, and mice, have been employed in pathogenesis studies of SARS-CoV-2. These animals could be infected by native SARS-CoV-2 virus (Blue color viral particles) and exhibit significant pathophysiological changes resembling COVID-19. **B** Generation of mouse-adapted SARS-CoV-2 virus. Intranasal inoculation of human SARS-CoV-2 isolates is carried out (blue viral particles) in wildtype BALBc/J mice. Mouse lungs are harvested, and the supernatants of the lung tissue homogenates are intranasally administered into naïve mice. The process is repeated for 6 passages minimum to achieve mouse adaptability (green viral particles). Method of passaging and generation of mouse-adapted viral strain has also been successful in C57B6/J mice (brown viral particles). **C** Human ACE2 expressing adenovirus (Adv) vectors are delivered intranasally to overexpress ACE2 in C57B6/J mouse lungs. After 48 h, intranasal inoculation of human SARS-CoV-2 isolates is carried out (blue viral particles) to establish infectivity.

human COVID-19 pathogenesis, indicating the feasibility of using these animals as preclinical models to study pathogenesis of SARS-CoV-2 infection. However, additional nonhuman primate models are needed to resemble severe COVID-19.

Murine-Adapted SARS-CoV-2

Laboratory mouse strains are not at all susceptible to native SARS-CoV-2 infection [95]. Thus, the development of murine-adapted SARS-CoV-2 is crucial to recapitulate the processes of viral entry and pathogenesis without altering the genetic framework of experimental animals (Fig. 2b). SARS-CoV-2 has been adapted into a murine host by passaging the human SARS-CoV-2 in BALB/c mice up to 6 passages (MASCp6), demonstrating increased virulence in both aged and young BALB/c mice [96]. Besides passaging of SARS-CoV-2 in mice, point mutations of the viral genome Q493K, at the RBD, predictably binding to N31 residue of the mouse ACE2 receptor, facilitate the development of murine-adapted

(MA) SARS-CoV-2 stain [95]. Further passaging of the MA SARS-CoV-2 strain at passage 10 generated MA10 stain, which exhibited 10% mortality in 10-week young and 80% mortality in 1-year aged BALB/c mice, respectively, at day 7 post-intranasal challenge [97]. These murine-adapted SARS-CoV-2 stains have become instrumental in genetic studies of molecular pathways controlling the pathogenesis of COVID-19.

Human ACE2 Overexpression and SARS-CoV-2 in Mice

Since mACE2 does not efficiently bind to SARS-CoV-2, animal models expressing hACE2 have been investigated. For example, mice with h*ACE2* overexpression driven by the cytokeratin-18 promoter (K18-hACE2) showed susceptibility to SARS-CoV-2 infection marked by sufficient viral replication, impaired pulmonary function, and infiltration of immune cells [98]. Using reverse genetics, *Hfh4* (also known as *Foxj1*; a lung ciliated epithelial cell promoter)-promoter-driven hACE2 was expressed in the ciliated airway epithelium

and in neuronal cells of BALB/c mice thereby increasing SARS-CoV-2 binding *in vivo* and resulting in 40% mortality [95]. Intragastric and intranasal instillation of SARS-CoV-2 in C57BL/6 mice expressing h*ACE2* using CRISPR-Cas9 system resulted in similar high viral burden in the lungs, trachea, brain, and intestines in young and aged mice. Moreover, intragastrically infected mice also developed severe pulmonary pathology [99]. The CRISPR-Cas9 system proved to be more effective than the above-discussed methods as it replaced m*Ace2* gene in the loci GRC m38.p6 on chromosome X, with h*ACE2* gene, thereby ubiquitously expressing hACE2 in all tissues. Although viral burden was similar in both young and aged mice, inflammatory cell infiltration, alveolar damage, and focal hemorrhage were more pronounced in aged mice infected with SARS-CoV-2 [99]. Besides transgenic overexpression, Han K *et al.* delivered Ad5-h*ACE2* via oropharyngeal route and achieved a robust inflammatory response upon SARS-CoV-2 challenge. The authors confirmed that viral protein was localized on the pneumocytes in the septa, and the disease outcome as well as inflammatory response correlated with that in COVID-19 patients [100].

Infectious SARS-CoV-2 Clones and Luciferase Reporter Constructs to Study Pathogenesis and Host Response *in Vitro*

An infectious cDNA clone of SARS-CoV-2 has been developed to mimic human disease phenotype, and to engineer reporter viruses [101, 102]. Here, Dr. Pei-Yong Shi's laboratory employed a reverse-genetic system to clone the infectious SARS-CoV-2 ORFs cDNA, with monomeric NeonGreen (mNeoG) fluorescence tag to obtain mNeoG-fluorescence-tagged infectious clone of SARS-CoV-2 (icSARS-CoV-2-mNG) [101]. Infection of Vero-E6 cells with icSARS-CoV-2-mNG showed sustained infectivity with similar fluorescence for up to five passages (Fig. 3a). Another reporter virus was designed by the same group to use nanoluciferase signal as a measurement of viral load for the testing of anti-viral drugs or neutralization antibodies [103]. The advantage of the built-in infectious clone is resistance to any spontaneous mutations during passaging of SARS-CoV-2 isolates. Besides the reporter viruses, recombinant SARS-CoV-2 proteins expressing luciferase replicons of individual SARS-CoV-2 ORFs have been developed to reduce the risk of accidental exposure to infectious viral particles,

and therefore, these replicons can be used in BSL2 facility for potential antiviral studies [55, 104].

Pseudoviruses and hACE2 Overexpression in SARS-CoV-2 Pathogenesis Studies *in Vitro*

Pseudoviruses such as vesicular stomatitis virus (VSV) and polinton-like virus (pLV) have been employed as SARS-CoV-2 spike protein-expressing vectors in understanding the strategies of the spike protein binding to the host receptors, such as heparan sulfate, ACE2, and TMPRSS2 [44, 105, 106]. In the VSV-SARS-CoV-2 Spike expression system *in vitro* (Fig. 3b), greater infectivity and host response were observed in human lung adenocarcinoma cells, Calu-3, human colorectal epithelial cancer cells, Caco-2, and monkey kidney epithelial cells, Vero-E6, in comparison to ACE-2 overexpressing fibroblast cells HEK293, and BHK-1 [44, 107]. More importantly, neutralization of the VSV-SARS-CoV-2 Spike pseudo vectors with soluble-form of human ACE2 abrogated the infectivity in the tested cells [44, 107]. Several studies employed over-expression of ACE2 (Fig. 3c) in human cell lines including A549, HeLa-cells, and BHK-1 fibroblasts to increase susceptibility to SARS-CoV-2 infection *in vitro* [33, 90].

POTENTIAL ANTI-INFLAMMATORY PATHWAYS INVOLVED IN COVID-19

COVID-19 pathophysiology is accompanied by hypoxic conditions due to pulmonary edema and impaired gas exchange [108]. Hypoxia inducible factors (HIF) are crucial for the adaptation to hypoxic conditions [109]. Figure 4 illustrates the process of stabilization of HIF1α under hypoxic conditions. Several studies, including those from our laboratory, have demonstrated the important roles of hypoxia-inducible factors [110, 111], especially HIF1α, in modulating inflammation during acute organ injury, including acute lung injury [112–122]. HIF have been shown to inhibit SARS-CoV-2 replication. A recent study by Dr. Jane McKeating *et al.* demonstrated that hypoxia and pharmacologic HIF stabilization inhibits SARS-CoV-2 replication in pulmonary epithelial cells *in vitro* by reducing the expression of ACE2 and inhibiting viral RNA replication [123]. Collectively, the current knowledge of the role of HIF in ARDS and viral pneumonia points to a lung-protective role of HIF in SARS-CoV-2-associated
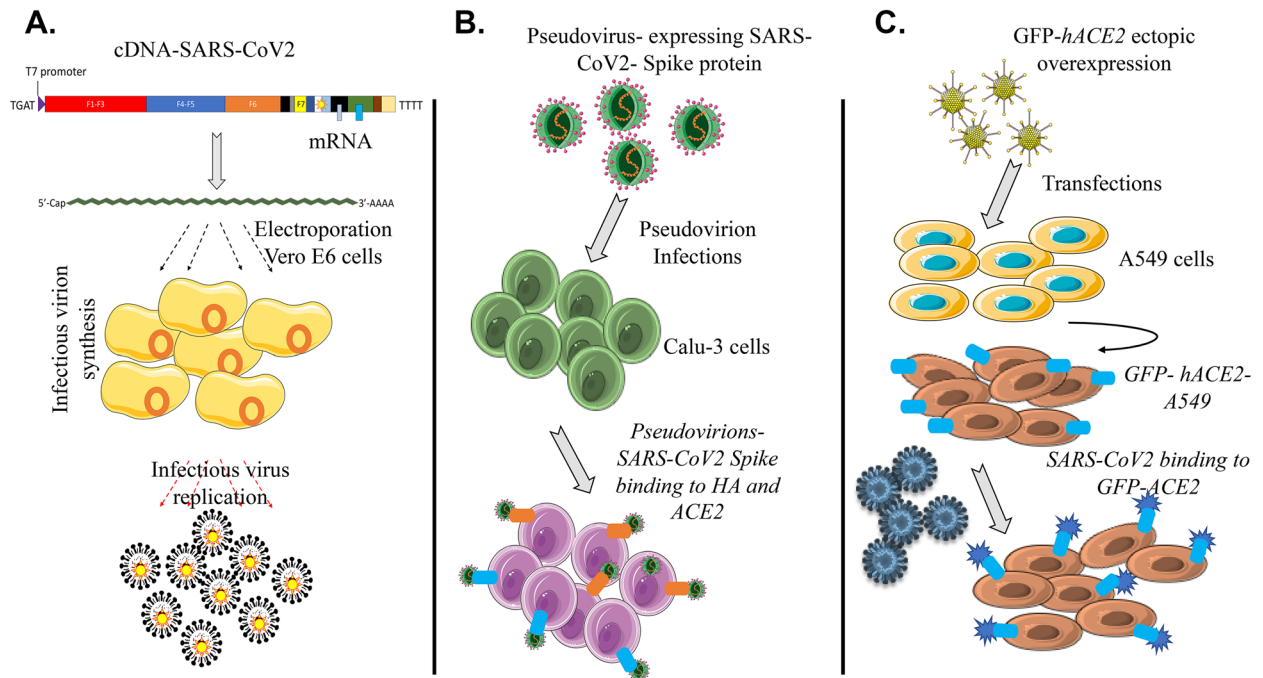
Fig. 3 Experimental strategies to study SARS-CoV-2 infection and COVID-19-like disease *in vitro*. **A** Generation of recombinant infectious clones by reverse genetics method. SARS-CoV-2 viral RNA template is reverse transcribed to get 11 sequential cDNA fragments of the ~ 29 Kb viral genome, with an eGFP-tag expressing fragment on the ORF11. The fragments are carefully ligated and *in vitro* transcribed to form a full-length recombinant mRNA. The full-length recombinant RNA is introduced into Vero-E6 cells by electroporation. The infected Vero-E6 cells are harvested after 48–72 h and the infectious clones of eGFP-expressing virions are isolated. **B** Generation of pseudovirus expressing spike protein from SARS-CoV-2 virus. Pseudoviruses such as vesicular stomatitis virus (VSV) and polinton-like virus (pLV) have been employed as SARS-CoV-2 spike protein-expressing vectors in understanding the strategies of the spike protein binding to the host receptors, such as heparan sulfate, ACE2 and TMPRSS2 in human lung adenocarcinoma cells, Calu-3, human colorectal epithelial cancer cells, Caco-2, and monkey kidney epithelial cells, Vero-E6. C. Ectopic overexpression of hACE2 in human type-2 alveolar epithelial cells, A549, and HeLa-cells and BHK-1 fibroblasts results in susceptibility of SARS-CoV-2 infection *in vitro*.

ARDS, and importantly, a clinical trial using vadadustat, a HIF activator, is currently ongoing (NCT04478071).

The role of purinergic signaling has been studied extensively in acute and chronic mucosal inflammation (Fig. 5) [124–137]. The role of ectonucleotidases CD39 (ectonucleoside triphosphate diphosphohydrolase-1) and CD73 (ecto-5′-nucleotidase) in the pathophysiology of COVID-19 remained speculative although their functions in the modulation of extracellular ATP hydrolysis and adenosine signaling in other inflammatory conditions indicate potential involvement. CD73 is decreased on CD8 T cells and NKT cells in peripheral blood and CD73-CD8 T cells and NK cells have higher level of cytotoxicity [137]. A humanized anti-CD73 monoclonal antibody, AK119, has been evaluated in healthy subjects as a potential treatment for COVID-19 (NCT04516564). A recent study by Dr. M. Serena Longhi's team reveals that ectonucleotidases CD39

(ectonucleoside triphosphate diphosphohydrolase-1) is increased in PBMC of severe COVID-19 cases, indicating potential T cell exhaustion [138]. Additionally, adenosine signaling has been investigated extensively in the setting of acute organ injury and inflammatory diseases including ARDS [124, 125, 139–144]. Indeed, several pilot clinical trials suggested inhaled adenosine as a safe therapeutic intervention for COVID-19 with potential for clinical benefit [145, 146], supporting the feasibility of large-scale randomized clinical trials. Together, the potential impact of purinergic signaling in COVID-19-related ARDS warrants further investigations.

Previous studies have indicated the microRNAs are crucial player during immunopathogenesis [147–154], including acute lung injury and ARDS [154–156]. Earlier studies utilizing computational prediction and in silico analysis identified several microRNA clusters that
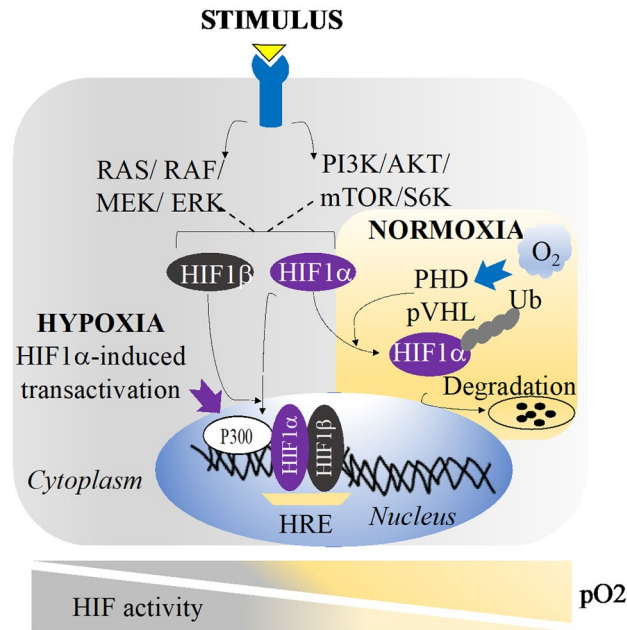
Fig. 4 Stabilization of hypoxia inducible factor (HIF). Growth factor-stimulated cellular signaling via downstream Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways leads to transcription of HIF1a. Under normal oxygen levels (normoxia), HIF1a protein is subjected to hydrolysis by prolyl hydroxylase (PHD) and proteasomal degradation involving tumor suppressor protein, von Hippel−Lindau protein (pVHL), and component of E3 ubiquitin protein ligase (Ub). Under hypoxic conditions, HIF1a is stabilized by suppression of ubiquitination process and dimerization with HIF1b, prior to nuclear translocation. The transcriptional coactivator p300 complexes with HIF1a/HIF1b dimer, binds to a 5 bp long hypoxia-response element [140] located on the promoter regions, and activates transcription of the target genes.

are associated with increased mortality of COVID-19 and viral-derived microRNAs targets several host genes [157]. Similarly, several coronavirus genome sequences including SARS-CoV-2 genome have been predicted as potential miRNA binding sites [158–160]. In addition, a recent study identified three circulating microRNAs (miR-423-5p, miR-23a-3p, and miR-195-5p) as signature microRNA predictor for SARS-CoV-2 infection [161]. However, their functional roles in viral replication and host responses are yet to be determined. In summary, future studies of the role of miRNAs in SARS-CoV-2 infection will provide potential therapeutic targeting for COVID-19.

EMERGING PHARMACOLOGIC INTERVENTIONS OF COVID-19 TREATMENT

Blocking Viral Entry

Administration of neutralization antibodies was proved important in the early phase of the pandemic with convalescent plasma donations. As of now, FDA has approved convalescent plasma treatment with high titer COVID-19 plasma containing Ortho Diagnostic's Vitros® anti-SARS-CoV-2 IgG, as well as low titer COVID-19 convalescent plasma [162]. However, despite massive NIH investments, convalescent serum has failed to demonstrate evidence of robust protection against severe disease. Besides convalescent plasma, currently, three antibodies have received Emergency USE Authorizations (EUAs) from the FDA to treat COVID-19 as an intravenous (IV) infusion. These antibodies are bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab (NIH, COVID-19 treatment guidelines). Bamlanivimab plus etesevimab were developed by Eli Lilly® and targets the spike protein from the SARS-CoV-2. Treatments of bamlanivimab plus etesevimab results in reduced incidence of hospitalization and death in high-risk COVID-19 patients (NCT04427501) [163]. Casirivimab plus imdevimab (REGEN-COV), an antibody cocktail developed by Regeneron®, reduces the risk of hospitalization or death in outpatients with COVID-19 (NCT04425629) prior to the emergence of Omicron
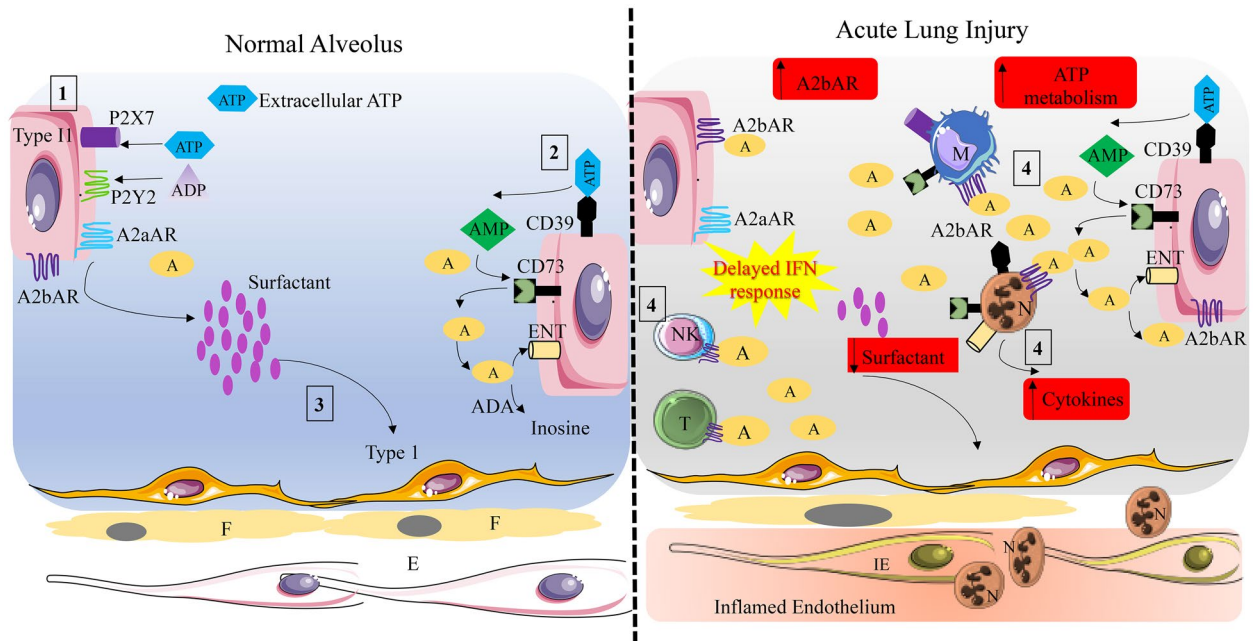
Fig. 5 Purinergic signaling and regulation of inflammation during acute lung injury. (1) Normal alveolus (left panel) shows extracellular ATP signaling through the purinergic receptors P2X7, whereas ADP binds to P2Y2 receptor. (2) Ectonucleotidase CD39 metabolizes ATP to generate AMP, and ectonucleotidase CD73 metabolizes AMP to release adenosine (A). Adenosine signaling occurs by binding to its receptors A1AR, A2aAR, ADORA2B, and A3AR; (only A2aAR and ADORA2B are shown for comparison to pathological conditions). (3) Under normal physiological conditions, ATP metabolism and adenosine signaling are sequestered by ENT1 and ENT2 that mobilize free adenosine from the extracellular compartment into the cytosol, and surfactant is released by type II pneumocytes to help the process of gas exchange and maintain alveolar homeostasis. During acute lung injury (right panel), excessive ATP is released into the extracellular space. Increased metabolism and adenosinergic signaling occur in the type II pneumocytes as well as in the immune cells (4) such as macrophages (M), neutrophils (N), natural killer cells (NK), and lymphocytes (T), controlling the dysregulated inflammation, delayed interferon (IFN) response, and extravasation of neutrophils.

variant [164]. Sotrovimab was developed by GlaxoSmithKline targeting a highly conserved epitope of sarbecoviruses including SARS-CoV-1. If given within 5 days after disease onset, sotrovimab halted COVID-19 progression leading to hospitalization or death (NCT04545060) [165].

Reducing Viral Replication-Anti-Viral Drugs in Practice

Due to their fundamentally important roles in host invasion, the key structural proteins of SARS-CoV-2 are actively studied as potential therapeutic targets. Remdesivir (GS-5734, Veklury) has been shown to be safe and effective in reducing the recovery time in hospitalized COVID-19 patients [103, 166]. The small molecule serves as an adenosine analog and stalls RdRp-mediated RNA synthesis [167]. It is the first experimental antiviral drug to be approved by FDA, particularly in young children and the elderly regardless of the severity of the disease.

Recently, molnupiravir, an oral antiviral drug from Merck®, was reported to provide clinical benefit in non-hospitalized COVID-19 patients [168]. Mechanistically, the active form of molnupiravir, β-D-N4-hydroxycytidine triphosphate, induces RNA mutagenesis as an analog of cytidine or uridine triphosphate, thus inducing SARS-CoV-2 mutagenesis during RNA synthesis in viral replication [169]. One potential concern is the associated risk of possibly predisposing to the emergence of new variants, which could be an unpredictable factor for the long-term impact of molnupiravir [170]. On the other hand, molnupiravir's ability to cause mutations in human cells could be another potential concern for long-term outcomes. The FDA has recently granted EAU for molnupiravir for the treatment of mild to moderate COVID-19.

Another small molecule antiviral drug that recently received FDA EUA is PAXLOVID from Pfizer®. PAXLOVID is an oral medication composed of PF-07321332

and low-dose ritonavir, a CYP3A4 isoenzyme inhibitor to prolong the half-life of PF-07321332 [171]. PF-07321332 targets the main protease of SARS-CoV-2 to hinder viral replication and pre-clinical studies suggested that oral PF-07321332 protects against SARS-CoV-2 infection in a mouse model [172]. The use of ritonavir in PAXLOVID will require further attention during COVID-19 management due to potentially enhancing the bioavailability of other prescribed or over the counter medications [171]. Thus, physicians should use caution and be aware of the interaction with other medications.

Targeting Endogenous Inflammatory Pathways

Reducing exacerbated inflammation by anti-inflammatory drugs, such as steroids, and blocking the clotting pathway activation by anticoagulants, such as heparins, are part of the standard practice in COVID-19 patients. For instance, dexamethasone (glucocorticoid) has been demonstrated to reduce mortality in hospitalized COVID-19 patients requiring respiratory support at randomization [173]. Tocilizumab (Actemra), an anti-IL6 receptor monoclonal antibody, has received EUA from FDA after a large-scale clinical trial indicated efficacy (NCT04372186) [174]. Sarilumab (Kevzara) is another monoclonal antibody targeting the IL-6 receptor that has not shown clinical benefit in a phase 3 trial [175]. However, additional studies are still ongoing in patients with severe COVID-19 pneumonia (NCT04386239). Janus Kinase inhibitors, baricitinib (Olumiant), have also received EUA from the FDA as treatment of COVID-19, as combined use of remdesivir and baricitinib confers clinical benefit in

Table 1 Potential Therapeutics Against Viral Hijacking of Immune System

Potential Therapeutics	Targets/pathways	Cellular networks involved	PMID/Clinical trial.gov Identifier
Adenosinergic signaling			
Adenosine	ADOR	Inflammation	NCT04588441
Dipridamole	ENT1/ENT2	Lymphocytes and platelet recovery	32318327/NCT04391179
	CD39	NK cell infiltration	
IPH52-mAb			31244820
MEDI9447-mAb	Anti-CD73	T effector cell function	27622077
BMS-986179-mAb			NCT02754141
CPI-444-mAb	A2aAR	Myeloid and lymphoid infiltration	30131376
AZD4635	A2bAR	T cell activation	32727810
PBF-509-mAb			30405415
MK-3814 small molecule			28490648
Hypoxia	PHDs inhibition		
Vadadustat			33283981
Roxadustat			30805897
Daprodustat			2880805
MicroRNAs			
miR126	Decrease autophagy, apoptosis, inflammation	Overexpression of miRNAs	27146208
miR146			30794808
miR150			31398659
miR223			28931657
miR181			29315794
miR127	Increase lung injury, inflammation	Repression of microRNAs	28765901
miR155			28125520
miR887			32321279
miR200			22189082

hospitalized patients with COVID-19 (NCT04401579) [176]. Regarding the modulation of coagulation pathways, the use of unfractionated heparin (UFH) and low molecular weight (LMWH) heparin is included to inhibit clotting factors Xa and thrombin by binding to the antithrombin [177]. In addition, antiplatelet agents such as nafamostat have been proposed to reduce SARS-CoV-2 fusion and TMPRSS2 mediated cleavage of the viral spike, resulting in lower viral burdens *in vitro* [178]. Administration of tissue-type plasminogen activator may also help in degrading fibrin clots and reduce the risk of micro clotting [179]. Finally, chronotherapy by precisely adjust the timing of the medication might be another interesting approach for the treatment of COVID-19 [180].

Vaccine Development-Prophylactics DNA, RNA, and Protein Vaccines

Vaccine development is crucial as a preventative measure in the control of respiratory pathogen infections such as influenza virus infection [181, 182]. As of February 2022, FDA has approved SARS-CoV-2 RNA vaccine from Pfizer-BioNTech and Moderna that have shown 90–95% protective efficacy in phase III clinical trials [183, 184]. The Pfizer-BioNTech mRNA vaccine, along with the Moderna vaccines, is already on the roll for global distribution and have been administered in the USA, the UK, and other countries. Besides mRNA vaccines, adenovirus vectors-based vaccines are also developed and studied for the prevention of COVID-19. A non-replicating viral vector (Adenovirus) encoding SARS-CoV-2 spike protein was developed in the UK (ChAdOx1 nCOV-19, AstraZeneca) that showed safety and efficacy from multiple trials [185, 186], and was approved in the UK and EU. Another adenovirus-based vaccines have been developed by Johnson and Johnson and confers protection of COVID-19, especially against the progression to severe diseases [187]. At the time that this review was drafted, 39.2% population worldwide and 58% population of US residents were fully vaccinated. Although the quick evolution of the SARS-CoV-2 virus may affect the effectiveness of vaccines, vaccines from companies like AstraZeneca, Pfizer/BioNTech, and Moderna have proved to provide protection against severe disease and death in the context of the Delta variant with only a slightly reduced efficacy [188–190]. The efficacy of COVID-19 vaccines need to be further evaluated against the Omicron variant. Of note,

antibody-dependent enhancement (ADE) has been noticed in SARS-CoV-1 and MERS-CoV infection when a non-neutralizing antibody facilitates viral entrance [191, 192], indicating a potential concern for vaccines against SARS-CoV-2. However, there is no evidence to support ADE in COVID-19 at this time [193, 194].

CONCLUSIONS AND CHALLENGES TO THE FIELD

Proper regulation of immune responses to environmental or pathogenic stimuli is crucial for the control and the resolution of tissue/organ injury. Previous studies have highlighted sophisticated pathways orchestrating immune responses in inflammatory conditions [121, 141, 195–207]. As the pathophysiology of COVID-19 started unraveling, the importance of inflammation has also been demonstrated in the pathogenesis of multiple organ injuries related to SARS-CoV-2 infection. Substantial progress has been made in the development of safe and efficacious vaccines against SARS-CoV-2. However, the emergence of multiple SARS-CoV-2 variants around the world and potential insufficient coverage of vaccinations in the overall population call for the development of effective therapeutic treatment options. As listed in Table 1, pharmacologic interventions on adenosinergic signaling and HIF signaling could be key steps to reduce acute lung injury in COVID-19 patients. Thus, therapeutic targeting of endogenous hypoxia-dependent anti-inflammatory pathways could potentially alleviate COVID-19-associated organ inflammation.

DECLARATIONS

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

REFERENCES

1. COVID-19 Genomics UK Consortium. 2020. COG-UK update on SARS-CoV-2 Spike mutations of special interest: Report 1 [19 December: COG-UK update on SARS-CoV-2 Spike mutations of special interest Report 1.

2. Ng, Y., Z. Li, Y.X. Chua, W.L. Chaw, Z. Zhao, B. Er, R. Pung, C.J. Chiew, D.C. Lye, D. Heng, et al. 2020. Evaluation of the effectiveness of surveillance and containment measures for the first 100 patients with COVID-19 in Singapore - January 2-February 29, 2020. MMWR. Morbidity and Mortality Weekly Report 69 (11): 307–311.

3. Pung, R., C.J. Chiew, B.E. Young, S. Chin, M.I. Chen, H.E. Clapham, A.R. Cook, S. Maurer-Stroh, M. Toh, C. Poh, et al. 2020. Investigation of three clusters of COVID-19 in Singapore: Implications for surveillance and response measures. Lancet 395 (10229): 1039–1046.

4. Wilder-Smith, A., C.J. Chiew, and V.J. Lee. 2020. Can we contain the COVID-19 outbreak with the same measures as for SARS? The Lancet Infectious Diseases 20 (5): e102–e107.

5. Heath, P.T., E.P. Galiza, D.N. Baxter, M. Boffito, D. Browne, F. Burns, D.R. Chadwick, R. Clark, C. Cosgrove, J. Galloway J, et al. 2021. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. The New England Journal of Medicine.

6. Heininger, U. 2021. Efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. The New England Journal of Medicine 385(3):288.

7. Polack, F.P., S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Perez Marc, E.D. Moreira, C. Zerbini, et al. 2020. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England Journal of Medicine 383 (27): 2603–2615.

8. Alves, J.G., and T.P. Lima. 2020. COVID-19 lethality in non-elderly individuals in cities with different Human Development Index. Tropical Doctor 49475520943716.

9. Ioannidis, J.P.A., C. Axfors, and D.G. Contopoulos-Ioannidis. 2020. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environmental Research 188:109890.

10. Lingappan, K., H. Karmouty-Quintana, J. Davies, B. Akkanti, and M.T. Harting. 2020. Understanding the age divide in COVID-19: Why are children overwhelmingly spared? American Journal of Physiology. Lung Cellular and Molecular Physiology 319 (1): L39–L44.

11. CDC. 2020. COVID-19 Pandemic Planning Scenarios.

12. Peckham, H., N.M. de Gruijter, C. Raine, A. Radziszewska, C. Ciurtin, L.R. Wedderburn, E.C. Rosser, K. Webb, and C.T. Deakin. 2020. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nature Communications 11 (1): 6317.

13. Holman, N., P. Knighton, P. Kar, J. O'Keefe, M. Curley, A. Weaver, E. Barron, C. Bakhai, K. Khunti, N.J. Wareham, et al. 2020. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: A population-based cohort study. The Lancet Diabetes and Endocrinology 8 (10): 823–833.

14. Rosenthal, N., Z. Cao, J. Gundrum, J. Sianis, and S. Safo. 2020. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. JAMA Network Open 3(12): e2029058.

15. Parohan, M., S. Yaghoubi, A. Seraji, M.H. Javanbakht, P. Sarraf, and M. Djalali. 2020. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of observational studies. The Aging Male 23 (5): 1416–1424.

16. Kompaniyets, L., A.B. Goodman, B. Belay, D.S. Freedman, M.S. Sucosky, S.J. Lange, A.V. Gundlapalli, T.K. Boehmer, and H.M. Blanck. 2021. Body Mass Index and Risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death - United States, March-December 2020. MMWR. Morbidity and Mortality Weekly Report 70 (10): 355–361.

17. Goffin, E., A. Candellier, P. Vart, M. Noordzij, M. Arnol, A. Covic, P. Lentini, S. Malik, L.J. Reichert, M.S. Sever, et al. 2021. COVID-19-related mortality in kidney transplant and haemodialysis patients: A comparative, prospective registry-based study. Nephrology, Dialysis, Transplantation 36 (11): 2094–2105.

18. O'Brien, J., K.Y. Du, and C. Peng. 2020. Incidence, clinical features, and outcomes of COVID-19 in Canada: Impact of sex and age. J Ovarian Res 13 (1): 137.

19. Gebhard, C., V. Regitz-Zagrosek, H.K. Neuhauser, R. Morgan, and S.L. Klein. 2020. Impact of sex and gender on COVID-19 outcomes in Europe. Biology of Sex Differences 11 (1): 29.

20. Hanidziar, D., and S.C. Robson. 2021. Hyperoxia and modulation of pulmonary vascular and immune responses in COVID-19. American Journal of Physiology. Lung Cellular and Molecular Physiology 320 (1): L12–L16.

21. Karmouty-Quintana, H., R.A. Thandavarayan, S.P. Keller, S. Sahay, L.M. Pandit, and B. Akkanti. 2020. Emerging mechanisms of pulmonary vasoconstriction in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) and potential therapeutic targets. *International Journal of Molecular Sciences* 21(21).

22. Jothimani, D., R. Venugopal, M.F. Abedin, I. Kaliamoorthy, and M. Rela. 2020. COVID-19 and the liver. *Journal of Hepatology* 73 (5): 1231–1240.

23. Kaltschmidt, B., A.D.E. Fitzek, J. Schaedler, C. Forster, C. Kaltschmidt, T. Hansen, F. Steinfurth, B.A. Windmoller, C. Pilger, C. Kong, *et al.* 2021. Hepatic vasculopathy and regenerative responses of the liver in fatal cases of COVID-19. *Clinical Gastroenterology and Hepatology* 19(8): 1726–1729 e1723.

24. Marjot, T., and G.J. Webb. 2021. Barritt ASt, Moon AM, Stamataki Z, Wong VW, Barnes E: COVID-19 and liver disease: Mechanistic and clinical perspectives. *Nature Reviews. Gastroenterology & Hepatology* 18 (5): 348–364.

25. Carvalho, T., F. Krammer, and A. Iwasaki. 2021. The first 12 months of COVID-19: A timeline of immunological insights. *Nature Reviews Immunology* 21 (4): 245–256.

26. Nalbandian, A., K. Sehgal, A. Gupta, M.V. Madhavan, C. McGroder, J.S. Stevens, J.R. Cook, A.S. Nordvig, D. Shalev, T.S. Sehrawat, *et al.* 2021. Post-acute COVID-19 syndrome. *Nature Medicine* 27 (4): 601–615.

27. Sudre, C.H., B. Murray, T. Varsavsky, M.S. Graham, R.S. Penfold, R.C. Bowyer, J.C. Pujol, K. Klaser, M. Antonelli, L.S. Canas, *et al.* 2021. Attributes and predictors of long COVID. *Nature Medicine* 27 (4): 626–631.

28. Cui, J., F. Li, and Z.L. Shi. 2019. Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology* 17 (3): 181–192.

29. Zhao, Y., Z. Zhao, Y. Wang, Y. Zhou, Y. Ma, and W. Zuo. 2020. Single-Cell RNA Expression Profiling of ACE2, the receptor of SARS-CoV-2. *American Journal of Respiratory and Critical Care Medicine* 202 (5): 756–759.

30. Letko, M., A. Marzi, and V. Munster. 2020. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiology* 5 (4): 562–569.

31. Letko, M., and V. Munster. 2020. Functional assessment of cell entry and receptor usage for lineage B beta-coronaviruses, including 2019-nCoV. *BioRxiv.*

32. Zhang, H., J.M. Penninger, Y. Li, N. Zhong, and A.S. Slutsky. 2020. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Medicine* 46 (4): 586–590.

33. Zhou, P., X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, *et al.* 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579 (7798): 270–273.

34. Gobeil, S.M., K. Janowska, S. McDowell, K. Mansouri, R. Parks, V. Stalls, M.F. Kopp, K. Manne, D. Li, and K. Wiehe, *et al.* 2021. Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity. *Science.*

35. Greaney, A.J., T.N. Starr, P. Gilchuk, S.J. Zost, E. Binshtein, A.N. Loes, S.K. Hilton, J. Huddleston, R. Eguia, K.H.D. Crawford, *et al.* 2021. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. *Cell Host & Microbe* 29(1): 44–57 e49.

36. Harvey, W.T., A.M. Carabelli, B. Jackson, R.K. Gupta, E.C. Thomson, E.M. Harrison, C. Ludden, R. Reeve, A. Rambaut, C.G.U. Consortium, *et al.* 2021. SARS-CoV-2 variants, spike mutations and immune escape. *Nature Reviews. Microbiology* 19(7): 409–424.

37. Lauring, A.S., P.N. Malani. 2021. Variants of SARS-CoV-2. *JAMA.*

38. Sander, A.L., A. Yadouleton, E.F. de Oliveira Filho, C. Tchibozo, G. Hounkanrin, Y. Badou, P. Adewumi, K.K. Rene, D. Ange, S. Sourakatou, *et al. 2021.* Mutations associated with SARS-CoV-2 variants of concern, benin, early 2021. *Emerging Infectious Diseases* 27(11).

39. Liu Y., J. Liu, B.A. Johnson, H. Xia, Z. Ku, C. Schindewolf, S.G. Widen, Z. An, S.C. Weaver, V.D. Menachery, *et al.* 2021. Delta spike P681R mutation enhances SARS-CoV-2 fitness over Alpha variant. *BioRxiv.*

40. Halfmann, P.J., S. Iida, K. Iwatsuki-Horimoto, T. Maemura, M. Kiso, S.M. Scheaffer, T.L. Darling, A. Joshi, S. Loeber, G. Singh, S.L. Foster, *et al.* 2022. SARS-CoV-2 Omicron virus causes attenuated disease in mice and hamsters. *Nature* Published online 21 January 2022.

41. Shuai, H., J.F. Chan, B. Hu, Y. Chai, T.T. Yuen, F. Yin, X. Huang, C. Yoon, J.C. Hu, H. Liu, J. Shi, *et al.* 2022. Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron. *Nature* Published online 21 January 2022.

42. Anthony, S.J., C.K. Johnson, D.J. Greig, S. Kramer, X. Che, H. Wells, A.L. Hicks, D.O. Joly, N.D. Wolfe, P. Daszak, *et al.* 2017. Global patterns in coronavirus diversity. *Virus Evolution* 3(1): vex012.

43. Guruprasad, L. 2020. Evolutionary relationships and sequence-structure determinants in human SARS coronavirus-2 spike proteins for host receptor recognition. *Proteins* 88 (11): 1387–1393.

44. Hoffmann, M., H. Kleine-Weber, S. Schroeder, N. Kruger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, *et al.* 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181(2): 271–280 e278.

45. Hassan, S.S., P.P. Choudhury, and B. Roy. 2020. SARS-CoV2 envelope protein: non-synonymous mutations and its consequences. *Genomics.*

46. Masters, P.S., L. Kuo, R. Ye, K.R. Hurst, C.A. Koetzner, and B. Hsue. 2006. Genetic and molecular biological analysis of protein-protein interactions in coronavirus assembly. *Advances in Experimental Medicine and Biology* 581: 163–173.

47. Hoffmann, M., H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, *et al.* 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181 (2): 271-280.e278.

48. Tay, M.Z., C.M. Poh, L. Renia, P.A. MacAry, and L.F.P. Ng. 2020. The trinity of COVID-19: Immunity, inflammation and intervention. *Nature Reviews Immunology* 20 (6): 363–374.

49. Xia, S., Q. Lan, S. Su, X. Wang, W. Xu, Z. Liu, Y. Zhu, Q. Wang, L. Lu, and S. Jiang. 2020. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion

in the presence or absence of trypsin. *Signal Transduction and Targeted Therapy* 5 (1): 92.

50. Bristow, M.R., L.S. Zisman, N.L. Altman, E.M. Gilbert, B.D. Lowes, W.A. Minobe, D. Slavov, J.A. Schwisow, E.M. Rodriguez, I.A. Carroll, et al. 2020. Dynamic regulation of SARS-Cov-2 binding and cell entry mechanisms in remodeled human ventricular myocardium. *JACC Basic to Translational Science* 5 (9): 871–883.

51. Shang, J., Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, and F. Li. 2020. Cell entry mechanisms of SARS-CoV-2. *Proceedings of the National Academy of Sciences of the United States of America* 117 (21): 11727–11734.

52. Li, S.W., C.Y. Wang, Y.J. Jou, S.H. Huang, L.H. Hsiao, L. Wan, Y.J. Lin, S.H. Kung, and C.W. Lin. 2016 SARS coronavirus papain-like protease inhibits the TLR7 signaling pathway through removing Lys63-linked polyubiquitination of TRAF3 and TRAF6. *International Journal of Molecular Sciences* 17(5).

53. Meylan, E., J. Tschopp, and M. Karin. 2006. Intracellular pattern recognition receptors in the host response. *Nature* 442 (7098): 39–44.

54. Salvi, V., H.O. Nguyen, F. Sozio, T. Schioppa, C. Gaudenzi, M. Laffranchi, P. Scapini, M. Passari, I. Barbazza, L. Tiberio, et al. 2006. SARS-CoV-2-associated ssRNAs activate inflammation and immunity via TLR7/8. *JCI Insight* 6(18).

55. Lei, X., X. Dong, R. Ma, W. Wang, X. Xiao, Z. Tian, C. Wang, Y. Wang, L. Li, L. Ren, et al. 2020. Activation and evasion of type I interferon responses by SARS-CoV-2. *Nature Communications* 11 (1): 3810.

56. Kouwaki, T., T. Nishimura, G. Wang, and H. Oshiumi. 2021. RIG-I-like receptor-mediated recognition of viral genomic RNA of severe acute respiratory syndrome coronavirus-2 and viral escape from the host innate immune responses. *Frontiers in Immunology* 12: 700926.

57. de Rivero Vaccari, J.C., W.D. Dietrich, R.W. Keane, and J.P. de Rivero Vaccari. 2020. The inflammasome in times of COVID-19. *Frontiers in Immunology* 11: 583373.

58. Jimenez-Dalmaroni, M.J., M.E. Gershwin, and I.E. Adamopoulos. 2016. The critical role of toll-like receptors–from microbial recognition to autoimmunity: A comprehensive review. *Autoimmunity Reviews* 15 (1): 1–8.

59. Lara, P.C., D. Macias-Verde, and J. Burgos-Burgos. 2020. Age-induced NLRP3 inflammasome over-activation increases lethality of SARS-CoV-2 pneumonia in elderly patients. *Aging & Disease* 11 (4): 756–762.

60. Ratajczak, M.Z., K. Bujko, A. Ciechanowicz, K. Sielatycka, M. Cymer, W. Marlicz, and M. Kucia. 2020. SARS-CoV-2 entry receptor ACE2 is expressed on very small CD45(-) precursors of hematopoietic and endothelial cells and in response to virus spike protein activates the Nlrp3 inflammasome. *Stem Cell Reviews and Reports*.

61. Vabret, N., G.J. Britton, C. Gruber, S. Hegde, J. Kim, M. Kuksin, R. Levantovsky, L. Malle, A. Moreira, M.D. Park, et al. 2020. Immunology of COVID-19: Current state of the science. *Immunity* 52 (6): 910–941.

62. Park, A., and A. Iwasaki. 2020. Type I and type III interferons - induction, signaling, evasion, and application to combat COVID-19. *Cell Host & Microbe* 27 (6): 870–878.

63. Thorne, L.G., M. Bouhaddou, A.K. Reuschl, L. Zuliani-Alvarez, B. Polacco, A. Pelin, J. Batra, M.V.X. Whelan, M.

Hosmillo, A. Fossati et al. 2021. Evolution of enhanced innate immune evasion by SARS-CoV-2. *Nature*.

64. Luo, W., J.W. Zhang, W. Zhang, Y.L. Lin, and Q. Wang. 2020. Circulating levels of IL-2, IL-4, TNF-alpha, IFN-gamma, and C-reactive protein are not associated with severity of COVID-19 symptoms. *Journal of Medical Virology*.

65. Zhang, F., J.R. Mears, L. Shakib, J.I. Beynor, S. Shanaj, I. Korsunsky, A. Nathan, L.T. and Donlin, S. Raychaudhuri. 2020. IFN- gamma and TNF- alpha drive a CXCL10 + CCL2 + macrophage phenotype expanded in severe COVID-19 and other diseases with tissue inflammation. *BioRxiv*.

66. Queisser, K.A., R.A. Mellema, E.A. Middleton, I. Portier, B.K. Manne, F. Denorme, E.J. Beswick, M.T. Rondina, R.A. Campbell, and A.C. Petrey. 2021. COVID-19 generates hyaluronan fragments that directly induce endothelial barrier dysfunction. *JCI Insight* 6(17).

67. Hellman, U., M.G. Karlsson, A. Engstrom-Laurent, S. Cajander, L. Dorofte, C. Ahlm, C. Laurent, and A. Blomberg. 2020. Presence of hyaluronan in lung alveoli in severe Covid-19: An opening for new treatment options? *Journal of Biological Chemistry* 295 (45): 15418–15422.

68. Codo, A.C., G.G. Davanzo, L.B. Monteiro, G.F. de Souza, S.P. Muraro, J.V. Virgilio-da-Silva, J.S. Prodonoff, V.C. Carregari, C.A.O. de Biagi Junior, F. Crunfli, et al. 2020. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1alpha/glycolysis-dependent axis. *Cell Metabolism* 32(3): 437–446 e435.

69. Boumaza, A., L. Gay, S. Mezouar, E. Bestion, A.B. Diallo, M. Michel, B. Desnues, D. Raoult, B. La Scola, P. Halfon, et al. 2020. Monocytes and macrophages, targets of SARS-CoV-2: the clue for Covid-19 immunoparalysis. *The Journal of Infectious Diseases*.

70. Liao, M., Y. Liu, J. Yuan, Y. Wen, G. Xu, J. Zhao, L. Cheng, J. Li, X. Wang, F. Wang, et al. 2020. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nature Medicine* 26 (6): 842–844.

71. Lee, J.S., J.Y. Koh, K. Yi, Y.I. Kim, S.J. Park, E.H. Kim, S.M. Kim, S.H. Park, Y.S. Ju, Y.K. Choi, et al. 2021. Single-cell transcriptome of bronchoalveolar lavage fluid reveals sequential change of macrophages during SARS-CoV-2 infection in ferrets. *Nature Communications* 12 (1): 4567.

72. Lee, J.S., S. Park, H.W. Jeong, J.Y. Ahn, S.J. Choi, H. Lee, B. Choi, S.K. Nam, M. Sa, J.S. Kwon, et al. 2020. Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Science Immunology* 5(49).

73. Victorino, F., D.K. Sojka, K.S. Brodsky, E.N. McNamee, J.C. Masterson, D. Homann, W.M. Yokoyama, H.K. Eltzschig, and E.T. Clambey. 2015. Tissue-resident NK cells mediate ischemic kidney injury and are not depleted by anti-Asialo-GM1 antibody. *The Journal of Immunology* 195 (10): 4973–4985.

74. Zheng, M., Y. Gao, G. Wang, G. Song, S. Liu, D. Sun, Y. Xu, and Z. Tian. 2020. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cellular & Molecular Immunology* 17 (5): 533–535.

75. Wang, W., X. Liu, S. Wu, S. Chen, Y. Li, L. Nong, P. Lie, L. Huang, L. Cheng, Y. Lin, et al. 2020. Definition and risks of cytokine release syndrome in 11 critically ill COVID-19

patients with pneumonia: Analysis of disease characteristics. *Journal of Infectious Diseases* 222 (9): 1444–1451.

76. Wilk, A.J., A. Rustagi, N.Q. Zhao, J. Roque, G.J. Martinez-Colon, J.L. McKechnie, G.T. Ivison, T. Ranganath, R. Vergara, T. Hollis, *et al.* 2020. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. *Nature Medicine* 26 (7): 1070–1076.

77. Weiskopf, D., K.S. Schmitz, M.P. Raadsen, A. Grifoni, N.M.A. Okba, H. Endeman, J.P.C. van den Akker, R. Molenkamp, M.P.G. Koopmans, E.C.M. van Gorp, *et al.* 2020. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Science Immunology* 5(48).

78. Ni, L., F. Ye, M.L. Cheng, Y. Feng, Y.Q. Deng, H. Zhao, P. Wei, J. Ge, M. Gou, X. Li, *et al.* 2020. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. *Immunity* 52(6): 971–977 e973.

79. Chen, G., D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, *et al.* 2020. Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of Clinical Investigation* 130 (5): 2620–2629.

80. Lei, L., H. Qian, X. Yang, X. Zhang, D. Zhang, T. Dai, R. Guo, L. Shi, Y. Cheng, B. Zhang, *et al.* 2020. The phenotypic changes of gammadelta T cells in COVID-19 patients. *Journal of Cellular and Molecular Medicine* 24 (19): 11603–11606.

81. Wolfel, R., V.M. Corman, W. Guggemos, M. Seilmaier, S. Zange, M.A. Muller, D. Niemeyer, T.C. Jones, P. Vollmar, C. Rothe, *et al.* 2020. Virological assessment of hospitalized patients with COVID-2019. *Nature* 581 (7809): 465–469.

82. Guo, C., B. Li, H. Ma, X. Wang, P. Cai, Q. Yu, L. Zhu, L. Jin, C. Jiang, J. Fang, *et al.* 2020. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm. *Nature Communications* 11 (1): 3924.

83. Ju, B., Q. Zhang, J. Ge, R. Wang, J. Sun, X. Ge, J. Yu, S. Shan, B. Zhou, S. Song, *et al.* 2020. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 584 (7819): 115–119.

84. Cao, W.C., W. Liu, P.H. Zhang, F. Zhang, and J.H. Richardus. 2007. Disappearance of antibodies to SARS-associated coronavirus after recovery. *New England Journal of Medicine* 357 (11): 1162–1163.

85. Payne, D.C., I. Iblan, B. Rha, S. Alqasrawi, A. Haddadin, M. Al Nsour, T. Alsanouri, S.S. Ali, J. Harcourt, C. Miao, *et al.* 2016. Persistence of antibodies against Middle East respiratory syndrome coronavirus. *Emerging Infectious Diseases* 22 (10): 1824–1826.

86. Cleary, S.J., S.C. Pitchford, R.T. Amison, R. Carrington, C.L. Robaina Cabrera, M. Magnen, M.R. Looney, E. Gray, and C.P. Page. 2020. Animal models of mechanisms of SARS-CoV-2 infection and COVID-19 pathology. *British Journal of Pharmacology* 177 (21): 4851–4865.

87. Cleary, S.J., M. Magnen, M.R. Looney, and C.P. Page. 2020. Update on animal models for COVID-19 research. *British Journal of Pharmacology* 177 (24): 5679–5681.

88. Shi, J., Z. Wen, G. Zhong, H. Yang, C. Wang, B. Huang, R. Liu, X. He, L. Shuai, Z. Sun, *et al.* 2020. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. *Science* 368 (6494): 1016–1020.

89. Schlottau, K., M. Rissmann, A. Graaf, J. Schon, J. Sehl, C. Wylezich, D. Hoper, T.C. Mettenleiter, A. Balkema-Buschmann, T. Harder, *et al.* 2020. SARS-CoV-2 in fruit bats, ferrets, pigs, and chickens: An experimental transmission study. *Lancet Microbe* 1 (5): e218–e225.

90. Blanco-Melo, D., B.E. Nilsson-Payant, W.C. Liu, S. Uhl, D. Hoagland, R. Moller, T.X. Jordan, K. Oishi, D. Panis, D. Sachs, *et al.* 2020. Imbalanced host response to SARS-CoV-2 Drives Development of COVID-19. *Cell* 181(5): 1036–1045 e1039.

91. Kim, Y.I., S.G. Kim, S.M. Kim, E.H. Kim, S.J. Park, K.M. Yu, J.H. Chang, E.J. Kim, S. Lee, M.A.B. Casel, *et al.* 2020. Infection and Rapid Transmission of SARS-CoV-2 in ferrets. *Cell Host & Microbe* 27(5): 704–709 e702.

92. Bertzbach, L.D., D. Vladimirova, K. Dietert, A. Abdelgawad, A.D. Gruber, N. Osterrieder, and J. Trimpert. 2020. SARS-CoV-2 infection of Chinese hamsters (Cricetulus griseus) reproduces COVID-19 pneumonia in a well-established small animal model. *Transboundary and Emerging Diseases*.

93. Le Bras, A. 2020. Syrian hamsters as a small animal model for COVID-19 research. *Laboratory Animals (NY)* 49 (8): 223.

94. Rockx, B., T. Kuiken, S. Herfst, T. Bestebroer, M.M. Lamers, B.B. Oude Munnink, D. de Meulder, G. van Amerongen, J. van den Brand, N.M.A. Okba, *et al.* 2020. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. *Science* 368 (6494): 1012–1015.

95. Dinnon, K.H., 3rd., S.R. Leist, A. Schafer, C.E. Edwards, D.R. Martinez, S.A. Montgomery, A. West, B.L. Yount Jr., Y.J. Hou, L.E. Adams, *et al.* 2020. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. *Nature* 586 (7830): 560–566.

96. Gu, H., Q. Chen, G. Yang, L. He, H. Fan, Y.Q. Deng, Y. Wang, Y. Teng, Z. Zhao, Y. Cui, *et al.* 2020. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science* 369 (6511): 1603–1607.

97. Leist, S.R., K.H. Dinnon, A. Schafer, L.V. Tse, K. Okuda, Y.J. Hou, A. West, C.E. Edwards, W. Sanders, E.J. Fritch, *et al.* 2020. A mouse-adapted SARS-CoV-2 induces acute lung injury and mortality in standard laboratory mice. *Cell* 183(4): 1070–1085 e1012.

98. Winkler, E.S., A.L. Bailey, N.M. Kafai, S. Nair, B.T. McCune, J. Yu, J.M. Fox, R.E. Chen, J.T. Earnest, S.P. Keeler, *et al.* 2020. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. *Nature Immunology* 21 (11): 1327–1335.

99. Sun, S.H., Q. Chen, H.J. Gu, G. Yang, Y.X. Wang, X.Y. Huang, S.S. Liu, N.N. Zhang, X.F. Li, R. Xiong, *et al.* 2020. A mouse model of SARS-CoV-2 infection and pathogenesis. *Cell Host & Microbe* 28(1): 124–133 e124.

100. Han, K., R.V. Blair, N. Iwanaga, F. Liu, K.E. Russell-Lodrigue, Z. Qin, C.C. Midkiff, N.A. Golden, L.A. Doyle-Meyers, M.E. Kabir, *et al.* 2020. Lung Expression of human ACE2 sensitizes the mouse to SARS-CoV-2 infection. *American Journal of Respiratory Cell and Molecular Biology*.

101. Xie, X., A. Muruato, K.G. Lokugamage, K. Narayanan, X. Zhang, J. Zou, J. Liu, C. Schindewolf, N.E. Bopp, P.V. Aguilar, *et al.* 2020. An Infectious cDNA Clone of SARS-CoV-2. *Cell Host & Microbe* 27(5): 841–848 e843.

102. Vanderheiden A., P. Ralfs, T. Chirkova, A.A. Upadhyay, M.G. Zimmerman, S. Bedoya, H. Aoued, G.M. Tharp, K.L. Pellegrini, C. Manfredi *et al.* 2020. Type I and type III interferons restrict SARS-CoV-2 infection of human airway epithelial cultures. *Journal of Virology* 94(19).

103. Xie, X., A.E. Muruato, X. Zhang, K.G. Lokugamage, C.R. Fontes-Garfias, J. Zou, J. Liu, P. Ren, M. Balakrishnan, T. Cihlar, *et al.* 2020. A nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19. *Nature Communications* 11 (1): 5214.

104. Xia, H., Z. Cao, X. Xie, X. Zhang, J.Y. Chen, H. Wang, V.D. Menachery, R. Rajsbaum, and P.Y. Shi. 2020. Evasion of type I interferon by SARS-CoV-2. *Cellular Reprogramming* 33(1): 108234.

105. Nie, J., Q. Li, J. Wu, C. Zhao, H. Hao, H. Liu, L. Zhang, L. Nie, H. Qin, M. Wang, *et al.* 2020. Establishment and validation of a pseudovirus neutralization assay for SARS-CoV-2. *Emerg Microbes Infect* 9 (1): 680–686.

106. Tandon, R., J.S. Sharp, F. Zhang, V.H. Pomin, N.M. Ashpole, D. Mitra, M.G. McCandless, W. Jin, H. Liu, P. Sharma, *et al.* 2021. Effective inhibition of SARS-CoV-2 entry by heparin and enoxaparin derivatives. *Journal of Virology* 95(3).

107. Ou, X., Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, *et al.* 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nature Communications* 11 (1): 1620.

108. Del Vecchio, L., and F. Locatelli. 2020. Hypoxia response and acute lung and kidney injury: Possible implications for therapy of COVID-19. *Clinical Kidney Journal* 13 (4): 494–499.

109. Colgan, S.P., and H.K. Eltzschig. 2012. Adenosine and hypoxia-inducible factor signaling in intestinal injury and recovery. *Annual Review of Physiology* 74: 153–175.

110. Berg, N.K., J. Li, B. Kim, T. Mills, G. Pei, Z. Zhao, X. Li, X. Zhang, W. Ruan, H.K. Eltzschig, *et al.* 2021. Hypoxia-inducible factor-dependent induction of myeloid-derived netrin-1 attenuates natural killer cell infiltration during endotoxin-induced lung injury. *FASEB Journal* 35(4): e21334.

111. Li, J., C. Conrad, T.W. Mills, N.K. Berg, B. Kim, W. Ruan, J.W. Lee, X. Zhang, X. Yuan, and H.K. Eltzschig. 2021. PMN-derived netrin-1 attenuates cardiac ischemia-reperfusion injury via myeloid ADORA2B signaling. *The Journal of Experimental Medicine* 218(6).

112. Eckle, T., E.M. Kewley, K.S. Brodsky, E. Tak, S. Bonney, M. Gobel, D. Anderson, L.E. Glover, A.K. Riegel, S.P. Colgan, *et al.* 2014. Identification of hypoxia-inducible factor HIF-1A as transcriptional regulator of the A2B adenosine receptor during acute lung injury. *Journal of immunology (Baltimore, Md : 1950)* 192(3): 1249–1256.

113. Vohwinkel, C.U., S. Hoegl, and H.K. Eltzschig. 2015. Hypoxia signaling during acute lung injury. *Journal of Applied Physiology (1985)* 119(10): 1157–1163.

114. Eltzschig, H.K., and P. Carmeliet. 2011. Hypoxia and inflammation. *New England Journal of Medicine* 364 (7): 656–665.

115. Shomento, S.H., C. Wan, X. Cao, M.C. Faugere, M.L. Bouxsein, T.L. Clemens, and R.C. Riddle. 2010. Hypoxia-inducible factors 1alpha and 2alpha exert both distinct and overlapping functions in long bone development. *Journal of Cellular Biochemistry* 109 (1): 196–204.

116. Yuan, X., J.W. Lee, J.L. Bowser, V. Neudecker, S. Sridhar, and H.K. Eltzschig. 2018. Targeting hypoxia signaling for perioperative organ injury. *Anesthesia and Analgesia* 126 (1): 308–321.

117. Vohwinkel, C.U., E.J. Coit, N. Burns, H. Elajaili, D. Hernandez-Saavedra, X. Yuan, T. Eckle, E. Nozik, R.M. Tuder, and H.K. Eltzschig. 2021. Targeting alveolar-specific succinate dehydrogenase A attenuates pulmonary inflammation during acute lung injury. *FASEB Journal* 35(4): e21468.

118. Lee, J.W., M. Koeppen, S.W. Seo, J.L. Bowser, X. Yuan, J. Li, M. Sibilia, A.V. Ambardekar, X. Zhang, T. Eckle, *et al.* 2020. Transcription-independent induction of ERBB1 through hypoxia-inducible factor 2A provides cardioprotection during ischemia and reperfusion. *Anesthesiology* 132 (4): 763–780.

119. Koeppen, M., T. Eckle, and H.K. Eltzschig. 2011. The hypoxia-inflammation link and potential drug targets. *Current Opinion in Anaesthesiology* 24 (4): 363–369.

120. Haeberle, H.A., C. Durrstein, P. Rosenberger, Y.M. Hosakote, J. Kuhlicke, V.A. Kempf, R.P. Garofalo, H.K. and Eltzschig. 2008. Oxygen-independent stabilization of hypoxia inducible factor (HIF)-1 during RSV infection. *PLoS One* 3(10): e3352.

121. Poth, J.M., K. Brodsky, H. Ehrentraut, A. Grenz, and H.K. Eltzschig. 2013. Transcriptional control of adenosine signaling by hypoxia-inducible transcription factors during ischemic or inflammatory disease. *Journal of Molecular Medicine (Berlin, Germany)* 91 (2): 183–193.

122. Ju, C., S.P. Colgan, and H.K. Eltzschig. 2016. Hypoxia-inducible factors as molecular targets for liver diseases. *Journal of Molecular Medicine (Berlin, Germany)* 94 (6): 613–627.

123. Wing, P.A.C., T.P. Keeley, X. Zhuang, J.Y. Lee, M. Prange-Barczynska, S. Tsukuda, S.B. Morgan, A.C. Harding, I.L.A. Argles, S. Kurlekar, *et al.* 2021. Hypoxic and pharmacological activation of HIF inhibits SARS-CoV-2 infection of lung epithelial cells. *Cell Reprogramming* 35(3): 109020.

124. Bowser, J.L., J.W. Lee, X. Yuan, and H.K. Eltzschig. 2017. The hypoxia-adenosine link during inflammation. *Journal of Applied Physiology (1985)*, 123(5): 1303–1320.

125. Le, T.T., N.K. Berg, M.T. Harting, X. Li, H.K. Eltzschig, and X. Yuan. 2019. Purinergic signaling in pulmonary inflammation. *Frontiers in Immunology* 10: 1633.

126. Li, X., N.K. Berg, T. Mills, K. Zhang, H.K. Eltzschig, and X. Yuan. 2019. Adenosine at the interphase of hypoxia and inflammation in lung injury. *Frontiers in Immunology* 11: 604944.

127. Yuan, X., D. Ferrari, T. Mills, Y. Wang, A. Czopik, M.F. Doursout, S.E. Evans, M. Idzko, and H.K. Eltzschig. 2021. Editorial: purinergic signaling and inflammation. *Frontiers in Immunology* 12: 699069.

128. Deaglio, S., K.M. Dwyer, W. Gao, D. Friedman, A. Usheva, A. Erat, J.F. Chen, K. Enjyoji, J. Linden, M. Oukka, *et al.* 2007. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *Journal of Experimental Medicine* 204 (6): 1257–1265.

129. Eltzschig, H.K., M.V. Sitkovsky, and S.C. Robson. 2012. Purinergic signaling during inflammation. *New England Journal of Medicine* 367 (24): 2322–2333.

130. Longhi, M.S. L. Feng, and S.C. Robson. 2021. Targeting ecto-nucleotidases to treat inflammation and halt cancer development in the gut. *Biochemical Pharmacology* 187: 114417.

131. Harshe, R.P., A. Xie, M. Vuerich, L.A. Frank, B. Gromova, H. Zhang, R.J. Robles, S. Mukherjee, E. Csizmadia, E. Kokkotou, *et al.* 2020. Endogenous antisense RNA curbs CD39 expression in Crohn's disease. *Nature Communications* 11 (1): 5894.

132. Dwyer, K.M., B.K. Kishore, and S.C. Robson. 2020. Conversion of extracellular ATP into adenosine: A master switch in renal health and disease. *Nature Reviews. Nephrology* 16 (9): 509–524.

133. Karmouty-Quintana, H., Y. Xia, and M.R. Blackburn. 2013. Adenosine signaling during acute and chronic disease states. *Journal of Molecular Medicine (Berlin, Germany)* 91 (2): 173–181.

134. Zhou, Y., D.J. Schneider, E. Morschl, L. Song, M. Pedroza, H. Karmouty-Quintana, T. Le, C.X. Sun, and M.R. Blackburn. 2011. Distinct roles for the A2B adenosine receptor in acute and chronic stages of bleomycin-induced lung injury. *The Journal of Immunology* 186 (2): 1097–1106.

135. He, T., E. Brocca-Cofano, D.G. Gillespie, C. Xu, J.L. Stock, D. Ma, B.B. Policicchio, K.D. Raehtz, C.R. Rinaldo, C. Apetrei, *et al.* 2015. Critical role for the adenosine pathway in controlling simian immunodeficiency virus-related immune activation and inflammation in gut mucosal tissues. *Journal of Virology* 89 (18): 9616–9630.

136. Aherne, C.M., C.B. Collins, C.R. Rapp, K.E. Olli, L. Perrenoud, P. Jedlicka, J.L. Bowser, T.W. Mills, H. Karmouty-Quintana, M.R. Blackburn, *et al.* 2018. Coordination of ENT2-dependent adenosine transport and signaling dampens mucosal inflammation. *JCI Insight* 3(20).

137. Ahmadi, P., P. Hartjen, M. Kohsar, S. Kummer, S. Schmiedel, J.H. Bockmann, A. Fathi, S. Huber, F. Haag, and J. Schulze Zur Wiesch. 2020. Defining the CD39/CD73 axis in SARS-CoV-2 infection: the CD73(-) phenotype identifies polyfunctional cytotoxic lymphocytes. *Cells* 9(8).

138. Wang, N., M. Vuerich, A. Kalbasi, J.J. Graham, E. Csizmadia, Z.J. Manickas-Hill, A. Woolley, C. David, E.M. Miller, K. Gorman, *et al.* Limited TCR repertoire and ENTPD1 dysregulation mark late-stage COVID-19. *iScience* 24(10): 103205.

139. Aherne, C.M., B. Saeedi, C.B. Collins, J.C. Masterson, E.N. McNamee, L. Perrenoud, C.R. Rapp, V.F. Curtis, A. Bayless, A. Fletcher, *et al.* 2015. Epithelial-specific A2B adenosine receptor signaling protects the colonic epithelial barrier during acute colitis. *Mucosal Immunology* 8 (6): 1324–1338.

140. Eckle, T., K. Hughes, H. Ehrentraut, K.S. Brodsky, P. Rosenberger, D.S. Choi, K. Ravid, T. Weng, Y. Xia, M.R. Blackburn, *et al.* 2013. Crosstalk between the equilibrative nucleoside transporter ENT2 and alveolar Adora2b adenosine receptors dampens acute lung injury. *FASEB journal : Official publication of the Federation of American Societies for Experimental Biology* 27 (8): 3078–3089.

141. Karmouty-Quintana, H., H. Zhong, L. Acero, T. Weng, E. Melicoff, J.D. West, A. Hemnes, A. Grenz, H.K. Eltzschig, T.S. Blackwell, *et al.* 2012. The A2B adenosine receptor modulates pulmonary hypertension associated with interstitial lung disease. *The FASEB Journal* 26 (6): 2546–2557.

142. Ehrentraut, H., J.A. Westrich, H.K. Eltzschig, and E.T. Clambey. 2012. Adora2b adenosine receptor engagement enhances regulatory T cell abundance during endotoxin-induced pulmonary inflammation. *PLoS One* 7(2): e32416.

143. Koeppen, M., T. Eckle, and H.K. Eltzschig. 2009. Selective deletion of the A1 adenosine receptor abolishes heart-rate slowing effects of intravascular adenosine *in vivo. PLoS One* 4(8): e6784.

144. Liu, H., Y. Zhang, H. Wu, A. D'Alessandro, G.G. Yegutkin, A. Song, K. Sun, J. Li, N.Y. Cheng, A. Huang, *et al.* 2016. Beneficial role of erythrocyte adenosine A2B receptor-mediated AMP-activated protein kinase activation in high-altitude hypoxia. *Circulation* 134 (5): 405–421.

145. Correale, P., M. Caracciolo, F. Bilotta, M. Conte, M. Cuzzola, C. Falcone, C. Mangano, A.C. Falzea, E. Iuliano, A. Morabito, *et al.* 2020. Therapeutic effects of adenosine in high flow 21% oxygen aereosol in patients with Covid19-pneumonia. *PLoS One* 15(10): e0239692.

146. Caracciolo M., P. Correale, C. Mangano, G. Foti, C. Falcone, S. Macheda, M. Cuzzola, M. Conte, A.C. Falzea, E. Iuliano, *et al.* 2021. Efficacy and effect of inhaled adenosine treatment in hospitalized COVID-19 patients. *Frontiers in Immunology* 12: 613070.

147. Nilsen, T.W. 2007. Mechanisms of microRNA-mediated gene regulation in animal cells. *Trends in Genetics* 23 (5): 243–249.

148. Yuan, X., N. Berg, J.W. Lee, T.T. Le, V. Neudecker, N. Jing, and H. Eltzschig. 2018. MicroRNA miR-223 as regulator of innate immunity. *Journal of leukocyte biology* 104 (3): 515–524.

149. Lu, W., R. You, X. Yuan, T. Yang, E.L. Samuel, D.C. Marcano, W.K. Sikkema, J.M. Tour, A. Rodriguez, F. Kheradmand, *et al.* 2015. The microRNA miR-22 inhibits the histone deacetylase HDAC4 to promote T(H)17 cell-dependent emphysema. *Nature Immunology* 16 (11): 1185–1194.

150. Cata, J.P., A. Gorur, X. Yuan, N.K. Berg, A.K. Sood, and H.K. Eltzschig. 2020. Role of micro-RNA for Pain after surgery: Narrative review of animal and human studies. *Anesthesia and Analgesia* 130 (6): 1638–1652.

151. Ju, C., M. Wang, E. Tak, B. Kim, C. Emontzpohl, Y. Yang, X. Yuan, H. Kutay, Y. Liang, D.R. Hall, *et al.* 2021. Hypoxia-inducible factor-1alpha-dependent induction of miR122 enhances hepatic ischemia tolerance. *The Journal of Clinical Investigation* 131(7).

152. Kim, B., V. Guaregua, X. Chen, C. Zhao, W. Yeow, N.K. Berg, H.K. Eltzschig, and X. Yuan. 2021. Characterization of a murine model system to study MicroRNA-147 during inflammatory organ injury. *Inflammation.*

153. Neudecker, V., K.S. Brodsky, S. Kreth, A.A. Ginde, and H.K. Eltzschig. 2016. Emerging roles for MicroRNAs in perioperative medicine. *Anesthesiology* 124 (2): 489–506.

154. Lee, T.J., X. Yuan, K. Kerr, J.Y. Yoo, D.H. Kim, B. Kaur, and H.K. Eltzschig. 2020. Strategies to modulate MicroRNA functions for the treatment of cancer or organ injury. *Pharmacological Reviews* 72 (3): 639–667.

155. Lee, L.K., L. Medzikovic, M. Eghbali, H.K. Eltzschig, and X. Yuan. 2020. The role of MicroRNAs in Acute respiratory distress syndrome and sepsis, from targets to therapies: A narrative review. *Anesthesia and Analgesia* 131 (5): 1471–1484.

156. Neudecker, V., K.S. Brodsky, E.T. Clambey, E.P. Schmidt, T.A. Packard, B. Davenport, T.J. Standiford, T. Weng, A.A. Fletcher, L. Barthel, *et al.* 2017. Neutrophil transfer of miR-223 to lung epithelial cells dampens acute lung injury in mice. *Science Translational Medicine* 9(408).

157. Khan, M.A., M.R.U. Sany, M.S. Islam, and A. Islam. 2020. Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19. *Frontiers in Genetics* 11: 765.

158. Canatan, D., and V. De Sanctis. 2020. The impact of MicroR-NAs (miRNAs) on the genotype of coronaviruses. *Acta Bio-Medica* 91 (2): 195–198.

159. Mukherjee, M., and S. Goswami. 2020. Global cataloguing of variations in untranslated regions of viral genome and prediction of key host RNA binding protein-microRNA interactions modulating genome stability in SARS-CoV-2. *PLoS One* 15(8): e0237559.

160. Nersisyan, S., M. Shkurnikov, A. Turchinovich, E. Knyazev, and A. Tonevitsky. 2020. Integrative analysis of miRNA and mRNA sequencing data reveals potential regulatory mechanisms of ACE2 and TMPRSS2. *PLoS One* 15(7): e0235987.

161. Farr, R.J., C.L. Rootes, L.C. Rowntree, T.H.O. Nguyen, L. Hensen, L. Kedzierski, A.C. Cheng, K. Kedzierska, G.G. Au, G.A. Marsh, *et al.* 2021. Altered microRNA expression in COVID-19 patients enables identification of SARS-CoV-2 infection. *PLoS Pathogens* 17(7): e1009759.

162. FDA. 2020. Recommendations for Investigational COVID-19 Convalescent Plasma.

163. Dougan, M., A. Nirula, M. Azizad, B. Mocherla, R.L. Gottlieb, P. Chen, C. Hebert, R. Perry, J. Boscia, B. Heller, *et al.* 2021. Bamlanivimab plus etesevimab in mild or moderate covid-19. *New England Journal of Medicine* 385 (15): 1382–1392.

164. Weinreich, D.M., S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, J. Xiao, A.T. Hooper, J.D. Hamilton, B.J. Musser, *et al.* 2021. REGEN-COV antibody combination and outcomes in outpatients with covid-19. *The New England Journal of Medicine* 385(23): e81.

165. Gupta, A., Y. Gonzalez-Rojas, E. Juarez, M. Crespo Casal, J. Moya, D.R. Falci, E. Sarkis, J. Solis, H. Zheng, N. Scott, *et al.* 2021. Early treatment for covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *New England Journal of Medicine* 385 (21): 1941–1950.

166. Beigel, J.H., K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, *et al.* 2020. Remdesivir for the treatment of Covid-19 - final report. *New England Journal of Medicine* 383 (19): 1813–1826.

167. Kokic, G., H.S. Hillen, D. Tegunov, C. Dienemann, F. Seitz, J. Schmitzova, L. Farnung, A. Siewert, C. Hobartner, and P. Cramer. 2021. Mechanism of SARS-CoV-2 polymerase stalling by remdesivir. *Nature Communications* 12 (1): 279.

168. Jayk Bernal, A., M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martin-Quiros, Y. Caraco, A. Williams-Diaz, M.L. Brown, *et al.* 2021. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *The New England Journal of Medicine*.

169. Kabinger, F., C. Stiller, J. Schmitzova, C. Dienemann, G. Kokic, H.S. Hillen, C. Hobartner, and P. Cramer. 2021. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nature Structural & Molecular Biology* 28 (9): 740–746.

170. Awadasseid, A., Y. Wu, Y. Tanaka, and W. Zhang. 2021. SARS-CoV-2 variants evolved during the early stage of the pandemic and effects of mutations on adaptation in Wuhan populations. *International Journal of Biological Sciences* 17 (1): 97–106.

171. Heskin, J., S.J.C. Pallett, N. Mughal, G.W. Davies, L.S.P. Moore, M. Rayment, and R. Jones. 2022. Caution required with use of ritonavir-boosted PF-07321332 in COVID-19 management. *Lancet* 399 (10319): 21–22.

172. Owen, D.R., C.M.N. Allerton, A.S. Anderson, L. Aschenbrenner, M. Avery, S. Berritt, B. Boras, R.D. Cardin, A. Carlo, K.J. Coffman, *et al.* 2021. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. *Science* 374 (6575): 1586–1593.

173. Group RC, P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, *et al.* 2021. Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine* 384 (8): 693–704.

174. Salama, C., J. Han, L. Yau, W.G. Reiss, B. Kramer, J.D. Neidhart, G.J. Criner, E. Kaplan-Lewis, R. Baden, L. Pandit, *et al.* 2021. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *New England Journal of Medicine* 384 (1): 20–30.

175. Lescure, F.X., H. Honda, R.A. Fowler, J.S. Lazar, G. Shi, P. Wung, N. Patel, and O. Hagino. 2021. Sarilumab C-GSG: Sarilumab in patients admitted to hospital with severe or critical COVID-19: A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory Medicine* 9 (5): 522–532.

176. Kalil, A.C., T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, *et al.* 2021. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *New England Journal of Medicine* 384 (9): 795–807.

177. Tang, N., H. Bai, X. Chen, J. Gong, D. Li, and Z. Sun. 2020. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *Journal of Thrombosis and Haemostasis* 18 (5): 1094–1099.

178. Yamamoto, M., M. Kiso, Y. Sakai-Tagawa, K. Iwatsuki-Horimoto, M. Imai, M. Takeda, N. Kinoshita, N. Ohmagari, J. Gohda, K. Semba, *et al.* 2020. The anticoagulant nafamostat potently inhibits SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system and viral infection *in vitro* in a cell-type-dependent manner. *Viruses* 12(6).

179. Wang, J., N. Hajizadeh, E.E. Moore, R.C. McIntyre, P.K. Moore, L.A. Veress, M.B. Yaffe, H.B. Moore, and C.D. Barrett. 2020. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series. *Journal of Thrombosis and Haemostasis* 18 (7): 1752–1755.

180. Tamimi, F., M. Abusamak, B. Akkanti, Z. Chen, S.H. Yoo, and H. Karmouty-Quintana. 2020. The case for chronotherapy in Covid-19-induced acute respiratory distress syndrome. *British Journal of Pharmacology* 177 (21): 4845–4850.

181. Wu, F., J.H. Huang, X.Y. Yuan, W.S. Huang, and Y.H. Chen. 2007. Characterization of immunity induced by M2e of influenza virus. *Vaccine* 25 (52): 8868–8873.

182. Wu, F., X.Y. Yuan, J. Li, and Y.H. Chen. 2009. The co-administration of CpG-ODN influenced protective activity of influenza M2e vaccine. *Vaccine* 27 (32): 4320–4324.

183. Thomas, S.J., E.D. Moreira Jr., N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Perez Marc, F.P. Polack, C. Zerbini, *et al.* 2021. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *New England Journal of Medicine* 385 (19): 1761–1773.

184. Jackson, L.A., E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, *et al.* 2020. An mRNA vaccine against SARS-CoV-2 - preliminary report. *The New England Journal of Medicine* 2021 Feb 4*; 384 (5): 403-416. https://doi.org/10.1056/NEJMoa2035389. Epub 2020 Dec 30. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine.

185. Folegatti, P.M., K.J. Ewer, P.K. Aley, B. Angus, S. Becker, S. Belij-Rammerstorfer, D. Bellamy, S. Bibi, M. Bittaye, E.A. Clutterbuck, *et al.* 2020. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 396 (10249): 467–478.

186. Voysey, M., S.A.C. Clemens, S.A. Madhi, L.Y. Weckx, P.M. Folegatti, P.K. Aley, B. Angus, V.L. Baillie, S.L. Barnabas, Q.E. Bhorat, *et al.* 2021. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 397 (10269): 99–111.

187. Sadoff, J., G. Gray, A. Vandebosch, V. Cardenas, G. Shukarev, B. Grinsztejn, P.A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, *et al.* 2021. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *The New England Journal of Medicine* 384(23): 2187–2201.

188. Shiehzadegan, S., N. Alaghemand, M. Fox, and V. Venketaraman. 2021. Analysis of the Delta variant B.1.617.2 COVID-19. *Clinical Practice* 11(4): 778–784.

189. Olson, S.M., M.M. Newhams, N.B. Halasa, A.M. Price, J.A. Boom, L.C. Sahni, K. Irby, T.C. Walker, S.P. Schwartz, P.S. Pannaraj, *et al.* 2021. Effectiveness of Pfizer-BioNTech mRNA vaccination against COVID-19 hospitalization among persons aged 12–18 years - United States, June-September 2021. *MMWR. Morbidity and Mortality Weekly Report* 70 (42): 1483–1488.

190. McBryde, E.S., M.T. Meehan, J.M. Caldwell, A.I. Adekunle, S.T. Ogunlade, M.A. Kuddus, R. Ragonnet, P. Jayasundara, J.M. Trauer, and R.C. Cope. 2021. Modelling direct and herd protection effects of vaccination against the SARS-CoV-2 Delta variant in Australia. *Medical Journal of Australia* 215 (9): 427–432.

191. Wan, Y., J. Shang, S. Sun, W. Tai, J. Chen, Q. Geng, L. He, Y. Chen, J. Wu, Z. Shi, *et al.* 2020. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *Journal of Virology* 94(5).

192. Yip, M.S., N.H. Leung, C.Y. Cheung, P.H. Li, H.H. Lee, M. Daeron, J.S. Peiris, R. Bruzzone, and M. Jaume. 2014. Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus. *Virol J* 11: 82.

193. Petousis-Harris, H. 2020. Assessing the safety of COVID-19 vaccines: A primer. *Drug Safety* 43 (12): 1205–1210.

194. Soiza, R.L., C. Scicluna, and E.C. Thomson. 2021. Efficacy and safety of COVID-19 vaccines in older people. *Age and Ageing* 50 (2): 279–283.

195. Shan, M., R. You, X. Yuan, M.V. Frazier, P. Porter, A. Seryshev, J.S. Hong, L.Z. Song, Y. Zhang, S. Hilsenbeck, *et al.* 2014. Agonistic induction of PPARgamma reverses cigarette smoke-induced emphysema. *The Journal of Clinical Investigation* 124 (3): 1371–1381.

196. You, R., W. Lu, M. Shan, J.M. Berlin, E.L. Samuel, D.C. Marcano, Z. Sun, W.K. Sikkema, X. Yuan, L. Song, *et al.* 2015. Nanoparticulate carbon black in cigarette smoke induces DNA cleavage and Th17-mediated emphysema. *eLife* 4: e09623.

197. Yuan, X., M. Shan, R. You, M.V. Frazier, M.J. Hong, R.A. Wetsel, S. Drouin, A. Seryshev, L.Z. Song, L. Cornwell, *et al.* 2015. Activation of C3a receptor is required in cigarette smoke-mediated emphysema. *Mucosal Immunology* 8 (4): 874–885.

198. Hong, M.J., B.H. Gu, M.C. Madison, C. Landers, H.Y. Tung, M. Kim, X. Yuan, R. You, A.A. Machado, B.E. Gilbert, *et al.* 2018. Protective role of gammadelta T cells in cigarette smoke and influenza infection. *Mucosal Immunology* 11 (3): 894–908.

199. Millien, V.O., W. Lu, G. Mak, X. Yuan, J.M. Knight, P. Porter, F. Kheradmand, and D.B. Corry. 2014. Airway fibrinogenolysis and the initiation of allergic inflammation. *Annals of the American Thoracic Society* 11 (Suppl 5): S277-283.

200. Yuan, X., C.Y. Chang, R. You, M. Shan, B.H. Gu, M.C. Madison, G. Diehl, S. Perusich, L.Z. Song, L. Cornwell, *et al.* 2019 Cigarette smoke-induced reduction of C1q promotes emphysema. *JCI Insight* 5.

201. Wang, Y., Y. Yang, M. Wang, S. Wang, J.M. Jeong, L. Xu, Y. Wen, C. Emontzpohl, C.L. Atkins, K. Duong, *et al.* 2021. Eosinophils attenuate hepatic ischemia-reperfusion injury in mice through ST2-dependent IL-13 production. *Science Translational Medicine* 13(579).

202. Eltzschig, H.K., S.K. Bonney, and T. Eckle. 2013. Attenuating myocardial ischemia by targeting A2B adenosine receptors. *Trends in Molecular Medicine* 19 (6): 345–354.

203. Mirakaj, V., C.A. Thix, S. Laucher, C. Mielke, J.C. Morote-Garcia, M.A. Schmit, J. Henes, K.E. Unertl, D. Kohler, and P. Rosenberger. 2010. Netrin-1 dampens pulmonary inflammation during acute lung injury. *American Journal of Respiratory and Critical Care Medicine* 181 (8): 815–824.

204. Mirakaj, V., J. Dalli, T. Granja, P. Rosenberger, and C.N. Serhan. 2014. Vagus nerve controls resolution and pro-resolving mediators of inflammation. *Journal of Experimental Medicine* 211 (6): 1037–1048.

205. Mirakaj, V., D. Gatidou, C. Potzsch, K. Konig, and P. Rosenberger. 2011. Netrin-1 signaling dampens inflammatory peritonitis. *The Journal of Immunology* 186 (1): 549–555.

206. Abdulnour, R.E., J.A. Howrylak, A.H. Tavares, D.N. Douda, K.M. Henkels, T.E. Miller, L.E. Fredenburgh, R.M. Baron, J. Gomez-Cambronero, and B.D. Levy. 2018. Phospholipase D isoforms differentially regulate leukocyte responses to acute lung injury. *Journal of Leukocyte Biology* 103 (5): 919–932.

207. Serhan, C.N., and B.D. Levy. 2018. Resolvins in inflammation: Emergence of the pro-resolving superfamily of mediators. *The Journal of Clinical Investigation* 128 (7): 2657–2669.