SARS-CoV-2 mediated lung inflammatory responses in host: targeting the cytokine storm for therapeutic interventions

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Received: 9 August 2020 / Accepted: 7 October 2020 / Published online: 16 October 2020
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Abstract
The recent exposure of novel coronavirus strain, severe acute respiratory syndrome (SARS-CoV-2) has spread to different countries at an alarming rate. Faster transmission rate and genetic modifications have provoked scientists to search for an immediate solution. With an increasing death rate, it becomes important to throw some light on the life cycle of the virus and its associated pathogenesis in the form of lung inflammation through cytokine storm (CS) production. This paper highlights the different stages of viral-mediated inflammatory responses in the host respiratory system. Previously, known anti-inflammatory drugs and therapeutic strategies that might show potential in controlling the CS of Coronavirus disease-2019 (COVID-19) is also mentioned in this study. Our critical analysis provides insights into the inflammation cycle induced in the lungs by early virus replication, downregulation and shedding of angiotensin-converting enzyme 2 (ACE2), and in the CS production. Identification of suitable targets within the inflammatory pathways for devising the therapeutic strategies useful in controlling the prognosis of COVID-19 finds a special mention in this article. However, antibody-dependent enhancement is the key aspect to consider before testing any drug/compound for therapeutic purposes. Our in-depth analysis would provide similarities and differences between the inflammatory responses induced by SARS-CoV and SARS-CoV-2, providing an excellent avenue to further look at how earlier outbreaks of coronaviruses were controlled and where new steps are required?

Keywords SARS-CoV-2 · COVID-19 · Lung inflammation · Cytokine storm · Therapeutic strategies · And antibody-dependent enhancement

Abbreviations

SARS-CoV Severe acute respiratory syndrome coronavirus
CoV Coronavirus
MERS-CoV Middle-east respiratory syndrome coronavirus
ARDS Acute respiratory distress syndrome
COVID-19 Coronavirus disease 2019
IL Interleukin
TNF Tumor necrosis factor
MCP Monocyte chemoattractant protein
IFNγ Interferon
MIP Macrophage inflammatory protein
G-CSF Granulocyte colony-stimulating factor
IP Interferon gamma induced protein
S Spike protein
M Membrane protein
N Nucleocapsid protein
E Envelope protein
Nsp Nonstructural protein
Rep Replicase gene
mRNA Messenger RNA
ORF Open reading frame
UTR Untranslated region
RBD Receptor-binding domain
ACE2 Angiotensin–converting enzyme 2
ER Endoplasmic reticulum
TMPRSS2 Transmembrane protease serine 2
DPP4 Dipeptidyl peptidase 4
FDA Food and Drug Administration
NLRP3 NOD-like protein receptor
RAS Renin-angiotensin system
TH1 TH1 helper cells
TH1 T helper cell
JAK Janus kinase

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Introduction

Multiple cases of pneumonia in patients were reported in December 2019 from Wuhan hospitals in China [1]. All the cases had a common history of exposure to the seafood market of the Hubei Province of China [2]. The virus was later found to be the new and the seventh strain of the Coronavirus (CoV)s family causing acute respiratory illnesses in humans [2]. Later, many confirmed cases did not show any travel history to the seafood market confirming the transmission of the virus that might have happened on a large scale [3].

CoVs belong to large families of enveloped viruses, having a positive-sense single-stranded RNA genome [4]. Bats are considered as the natural reservoirs of different CoVs [5]. The likely transmission to human species might have occurred through coming in direct contact of bats; however, multiple sources are claiming the presence of intermediate hosts responsible for the viral transmission [6]. In the case of Severe Acute Respiratory Syndrome (SARS-CoV-2), the genomic similarity of the receptor-binding domain (RBD) in the spike gene of the virus is greater to the pangolins (97.4%) than bats (89.2%) [5]. Also, 5 amino acids are similar in the RBD region of pangolins and SARS-CoV-2 whereas only one amino acid similarity exists between bats and the RBD domain of the virus, indicating pangolins as intermediate hosts through which human transmission has occurred [7, 8].

Although, the fatality rate of SARS-CoV-2 is much less than the previous outbreaks of CoVs the higher transmission rate generates a huge concern in controlling the rapid spreading of the disease [9, 10]. The periodical reoccurrence of novel CoVs after every decade is attributed to their broad existence in nature, diversity in genomic structures supporting their more frequent recombination, and in an increase of the human to animal interfacing interactions [2].

SARS-CoV-2 enters into the host for completing its life cycle [11]. Macrophages identify the pathogen-associated molecular patterns (PAMP) and trigger innate immunity [12, 13]. The severity of the disease is associated with the production of a cytokine storm (CS) by the macrophages inside the host cell post-viral attack [14]. Increased secretion of cytokines such as IL-1β, IP-10, MCP-1, IL-4, IL-10, and IFN-γ was similar as observed in SARS-CoV [15]. Also, patients at high risk of mortality show higher production of cytokines including IL-2, IL-10, GCSF, IP-10, MCP-1, IL-7, TNF-α, and MIP-1A [15].

Since, CS is an important concern in causing the virus associated lung inflammatory responses in the host, drugs targeting these pro-inflammatory cytokines may be an ideal strategy for overcoming the Coronavirus disease-2019 (COVID-19) pandemic [16, 17]. Several diagnostic and therapeutic approaches were undertaken to handle COVID-19 [18–22]. Here, we have reviewed different stages of inflammatory response mediated by the entry of SARS-CoV-2 in the human lung cells. Different therapeutic drugs that might show potential in targeting CS production are also described in detail. Figure 1 illustrates the plan of review, the areas that have been covered, and the highlights.

The viral-mediated inflammatory response in the host

The inflammatory response generated by SARS-CoV-2 results in the formation of acute lung injuries, pneumonia, and death [23]. These pathological conditions are the result of CS generated through early virus entry and replication [24]. There are different stages in which inflammatory and immune responses are generated once the virus enters into the host body through interaction with the Angiotensin-converting enzyme 2 (ACE2) receptors [25, 26]. (Fig. 2). An earlier study on SARS-CoV and its inflammatory pathways provide an important view of how the inflammation cycle might be happening in SARS-CoV-2 owning to their 80% genetic similarity.

Inflammation by early virus replication

The use of the same receptors ACE2 by SARS-CoV-2, as used by SARS-CoV, suggests the probability of targeting and infecting the same cells for initiating an infection [5, 27]. The replication of the virus is associated with apoptosis of epithelial and endothelial cells causing vascular leakage for the release of pro-inflammatory chemokines. Macrophages and lymphocytes may also undergo pyroptosis by this mechanism [28]. Pyroptosis occurs by the activation of viroporin 3a upon early viral replication which further activates NOD-like receptor protein 3 (NLRR3) [29]. This receptor causes increased synthesis of IL-1β in macrophages inducing pyroptosis and the release of pro-inflammatory cytokines [30]. The presence of pulmonary infiltrates of lymphocytes

| STAT   | Signal transducer and activator of transcription protein |
| ADCC   | Antibody-mediated cell cytotoxicity                      |
| ADE    | Antibody-dependent enhancement effect                    |
| FCR    | Fc receptor                                              |
| Nab    | Neutralizing antibodies                                  |
| TYK    | Tyrosine protein kinase                                  |
| CS     | Cytokine storm                                           |
| NCP    | Novel coronary pneumonia                                 |
| RA     | Rheumatoid arthritis                                     |
| TCZ    | Tocilizumab                                              |
| CXCR4  | C-X-C-chemokine receptor type 4                          |
| PAMP   | Pathogen-associated molecular patterns                    |
Fig. 1 Illustration of plans and highlights of the current study. Figure shows three major objectives of the study covered in this article and their associated key features summarizing the main findings.

Fig. 2 Immunopathogenesis initiated by SARS-CoV-2 replication in promoting the respiratory infection. The binding of SARS-CoV/SARS-CoV-2 on ACE2 of human lung cells causes increased viral uptake replication. This mediates apoptosis/pyroptosis of alveolar macrophages leading to the production of pro-inflammatory cytokines such as IL-1β and TNF-α. These cytokines further perform three actions: mediates ACE2 downregulation and shedding leading to loss of RAS, increased TH17 cell activation causing further secretion of other pro-inflammatory cytokines and causing infiltration of innate immune cells. These immune cells can further cause production of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) mediating TH17 cell function and leading to vascular permeability and leakage as the final steps of lung inflammation in the host cells post-viral attack. Abbreviations- Interleukin 1β (IL-1β), Tumor necrosis factor (TNF-α), Interleukin 17 (IL-17), Interleukin 21 (IL-21), Interleukin 22 (IL-22), Granulocyte–Macrophage Colony-Stimulating Factor (GM-CSF), T helper cells (TH 17), Renin-angiotensin system (RAS).
and cell bodies after apoptosis, has been found in 82.1% of the positive patients suggesting peripheral blood lymphopenia induced by SARS-CoV-2 [15, 31].

**Inflammation by downregulation of ACE2 receptors**

ACE2 receptors are present in the human lungs that lower the blood pressure by converting angiotensin II to angiotensin. SARS-CoV-2 uses this receptor for entry into the host cell and then downregulates its function [32, 33]. It also sheds the catalytic subunit of this receptor [34, 35]. The loss of the renin-angiotensin system (RAS) may enhance vascular permeability, accumulation of neutrophils, lung edema, inflammation, and acute lung injuries [36–38]. The enhancement in ACE2 shedding can be mediated by both SARS-CoV and SARS-CoV-2 infection and further release of inflammatory cytokines such as IL-1β and TNF-α by viral replication [39]. However, S protein-induced ACE2 shedding is mainly seen in SARS-CoV induced infection. Although these receptors are known to be used by other CoVs such as HNL-63-CoV, their pathogenies are restricted in causing common cold as no ACE2 shedding has been associated with their infection cycle [39]. Thus, this reflects the likelihood of ACE2 shedding in inducing acute lung injury and dysfunction of the respiratory system. This also suggests the pathogenicity behind SARS-CoV infection and now the novel strain, SARS-CoV-2 [26].

**Generation of cytokine storm**

Damages to muscular organs like lungs, heart, and kidneys have been reported in the presence of CS in the serum levels of the patients suffering from SARS-CoV-2 infection [15, 40]. Higher amounts of IL-1β, G-CSF, GM-CSF, MCP1, IFNγ, IP10, MIP1A, MIP1B, TNFα, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17 is found in non-ICU patients; however, elevated levels of IP10, IL-2, IL-7, IL-10, G-CSF, MIP1A, MCP1, and TNFα have been reported in critical patients in ICU [15]. TH17 and TH1 cells are primarily involved in imparting cytotoxicity (Fig. 3).

The two cytokines, IL-1β and TNFα promote the activity of TH17 cells inducing vascular permeability and leakage. This enables the secretion of other cytokines such as IL-17, IL-21, IL-22, and GM-CSF (also associated with TH1 cells in humans). All of these cytokines have profound roles in the induction of other pro-inflammatory cytokines mediating the inflammatory responses in the host cells. For example, IL-17 induces the synthesis of G-CSF required in the recruitment of neutrophils; in the synthesis of IL-1β, TNFα, and IL-6 producing symptoms such as fever; in...
matrix metalloproteinases that are actively engaged in damaging and remodeling of tissues; in chemokines KC, IL-8, MIP3A, IP10, and MIP2A that causes increased attraction and recruitment of immune infiltrates. IL-21 is required for the maintenance of TH17 cells and aids in the development of immune responses in the STAT-3 dependent manner from germinal centers. The upregulation of mucus, anti-apoptotic proteins, fibrinogens, LPS binding proteins, and serum amyloid A by IL-22 suggests its involvement in the formation of edema filled with mucus and fibers as observed in patients of SARS-CoV and SARS-CoV-2 [41, 42]. Higher numbers and expression of TH17 cells producing a CS was observed in critical patients of SARS-CoV-2 infection. However, the enhanced response of TH17 cells and IL-17 associated pathways are also detected in infections caused by SARS-CoV and MERS-CoV [43, 44]. Since TH17 cells have been predominately involved in generating CS, causing pulmonary edema and damage to the lungs, scientists have suggested the use of inhibitors of TH17 cells as an appropriate way of controlling the infection [25].

The TH17 cell differentiation begins by elevated levels of IL-6 and IL-23 cytokines which activate JAK2. JAK2 further activates a receptor which in turn activates a transcription factor called STAT3 and mediates the differentiation and cellular response of TH17 cells (Fig. 4a) [45]. Studies support the use of JAK2 inhibitors in controlling the TH17 cell function (Fig. 4b). STAT3 inhibitors may also be effective in inhibiting the TH17 cell responses (Fig. 4c) but their active role in the B cell activation pathway through IL-21 signals (Fig. 4d) limits their use as a therapeutic strategy for CS production. In other terms, inhibition of STAT-3 may protect the patient from CS but it can also lead to B cell inactivation and therefore STAT inhibition is not preferred for COVID-19 patients. JAK2 does not disrupt these signals hence, targeting this would be an ideal strategy in drug preparation [25]. The drug for JAK2 inhibition has been discussed in the subsequent sections in detail.

Anti-inflammatory drugs and strategies to COVID-19 treatment

Different therapeutic strategies can be used in controlling the respiratory infection. These could involve either the use of JAK inhibitors that block TH17 cell activation and can further stop the generation of CS [25]. The drugs that block the Fc receptors on macrophages so that no antibody-dependent enhancement (ADE) could occur may also be used in cases where ADE associated lung inflammation predominates during the drug delivery [26]. Moreover, anti-inflammatory drugs that directly target the specific or non-specific cytokines produced by SARS-CoV-2 pathogenesis in the host system might also play a significant role in COVID-19 treatment [46] (Table 1).

Some of the anti-inflammatory drugs that have previously been used in different diseases such as in rheumatoid arthritis (RA), cancers, and immunosuppressants during transplant might hold potential in controlling SARS-CoV-2 infection as well [70]. Many ongoing trials are currently under study whose full potential in reducing the cytokine storm of COVID-19 patients should be tested.

Fedratinib

Fedratinib is a Food and Drug Administration (FDA) approved drug that is known to inhibit JAK2 (a mediator of TH17 cell differentiation for producing the CS). Researchers tested its efficacy in controlling myeloproliferative neoplasms on cytokine products of TH17 cells. It was found that Fedratinib decreased the CS produced by TH17 cells without inhibiting the activities of JAK1, JAK3, and TYK2 required for antiviral immunity. Fedratinib along with IL23 resulted in much better efficiency in controlling TH17 cell differentiation. Besides, JAK2 the drug also showed a significant reduction in expression of IL-22 by TH17 cells and GF-CSF, a cytokine-dependent upon JAK2 for transducing its signals [71]. Therefore, a JAK2 inhibitor, Fedratinib plays an important role in reducing the cytokine load generated in the critical patients suffering from SARS-CoV-2 infection and may be used as an effective treatment for combating COVID-19 at the moment [25].

Tocilizumab

Tocilizumab (TCZ) is a recombinant monoclonal antibody designed to block both membrane-bound and soluble IL-6 receptors and their associated signaling pathways [46]. This drug has been previously used for rheumatic diseases and in treating the severe cytokine release syndrome which is a life-threatening disorder caused by immunotherapy in cancer patients [72]. Various clinical trials have supported the efficacy of TCZ in the treatment of novel coronavirus pneumonia (NCP). It has also shown a considerable antagonistic effect on the host reaction stimulated by acute respiratory distress syndrome (ARDS) associated with COVID-19 [51]. In a study of 20 patients, 400 mg of the dose was given intravenously. After a few days, fever and other symptoms of coronavirus were improved remarkably with better oxygenation capacity of the patient up to 75%. The lesions observed through CT scan were also improved in 90.5% patients and 52.6% of patients showed normal levels of peripheral lymphocytes. This study had raised a potential area for more such randomized trials in the treatment of COVID-19 (to be published). Another study performed on 21 critical cases of COVID-19 says

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one or two doses of TCZ has promoted better recovery of the patients with reduced risk of death [47]. Since no toxicity has been observed with its usage, Chinese health authorities have included TCZ for managing pneumonia associated with COVID-19. The timing of administration of this drug needs to be monitored as in some cases earlier administration of this drug proved to be better in reducing the IL-6 signaling [48].

### Emapalumab

Emapalumab is an IgG1 human monoclonal antibody that has a high affinity towards INF-γ [49]. This is an FDA approved drug for the treatment of multiple organ failure caused by hyper inflammation [50]. Blocking of this free and membrane-bound receptor could prevent the hyper-reaction of the host against SARS-CoV-2 [70].
Molecular and Cellular Biochemistry (2021) 476:675–687

**Fig. 4** Effect of JAK-2 and STAT-3 inhibitions in the regulation of TH17 cell differentiation and their consequences. a Shows the signaling of TH17 cells through the JAK-STAT pathway without the use of any inhibitors. Binding of IL-6 and IL-23 cytokines cause the dimerization of the receptor. This allows JAK-2 a receptor-bound enzyme to phosphorylate the tyrosine residues of the receptor for its activation. STAT-3 now interacts with the phosphorylated receptor with its SH2 domain and its dimerization occurs. The dimer travels to the nucleus and starts acting as a transcription factor. TH17 cell differentiation occurs through this mechanism leading to the formation of cytokine storm in COVID-19 patients. b Describes the effect of the JAK2 inhibitor on TH17 cell signaling. No phosphorylation of the receptors would occur in the absence of an active JAK2 and hence no STAT activation for transcription. TH17 cell differentiation could not occur and the patient may be cured for COVID-19 without the production of the cytokine storm. c Shows the effect of STAT-3 inhibitors on signaling of TH17 cells mediated by IL-6 and IL-23 ligands in the JAK-STAT pathway. Binding of IL-6 and IL-23 cytokines cause the dimerization of the receptor. This allows JAK-2 a receptor-bound enzyme to phosphorylate the tyrosine residues of the receptor for its activation. STAT-3 now interacts with the phosphorylated receptor with its SH2 domain. The use of inhibitors for STAT-3 now prevents STAT dimerization for acting as a transcription factor, as a result, no TH17 cell differentiation occurs through this mechanism, and no formation of cytokine storm in COVID-19 patients. d Describes the effect of STAT-3 inhibitors on B cell activation required for the antiviral immunity by IL-21 ligand in the JAK-STAT pathway. Binding of IL-21 cytokine causes the dimerization of the receptor. This allows JAK-1/3 a receptor-bound enzyme to phosphorylate the tyrosine residues of the receptor for its activation. STAT-3 now interacts with the phosphorylated receptor with its SH2 domain. The use of inhibitors for STAT-3 now prevents STAT dimerization for acting as a transcription factor, as a result, no B cell activation occurs through this mechanism, and no formation of immunity against SARS-CoV-2 infection. The red arrow indicates the target area for the action of drugs known as Fedritanib. (Shown in the orange box). Abbreviation: IL Interleukin, JAK Janus kinase, STAT signal transducer and activator of transcription, SH2 Src homology domain

### Infliximab and Etanercept

Defense mechanisms of the host after exposure to an antigen are often associated with the production of TNF-α, a pro-inflammatory cytokine produced by brain cells such as astrocytes and microglia, macrophages, endothelial cells, lymphoid cells, adipose tissue, and cardiac myocytes. They have profound roles in producing fever, in arresting the growth of cancer cells, and in inhibiting the viral replication upon their interaction with the host.

Infliximab is a monoclonal antibody that targets TNF-α and Etanercept is a protein that fuses with the TNF-α receptor causing its inactivation. The role of these drugs in RA and other immune disorders suggests their role in combating the main initiator TNF-α of CS in COVID-19 patients.

### Plerixafor

Plerixafor is an antagonist of CXCRL1, a receptor required for the chemotaxis of inflammatory cells such as monocytes, lymphocytes, and neutrophils. Plerixafor causes attenuation of TH17 cells and reduces the inflammatory cells to enter into the airway further reducing the levels of IL-4, IL-5, and IL-13 in the lungs preventing acute lung injuries.

### Mycophenolate

Mycophenolate contains mycophenolic acids which are being used as an immunosuppressive agent for the patients of kidney transplants. There are two ways through which this drug actions-in the first case it causes a reduction in the levels of guanosine and deoxyguanosine nucleotide by inhibiting an enzyme called inositol monophosphate dehydrogenase finally causing impairment in the activities of B and T lymphocytes. The other action of mycophenolate lies within its ability to inhibit the mRNA expression of various pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β. Earlier this has proved to possess a non-competitive inhibiting ability of Middle-east Respiratory Syndrome (MERS-CoV)- papain-like protease. The side effects of this drug have also been described involving diarrhea, urinary infections, and leukopenia.

### Anakinra

Anakinra is an antagonist of the IL-1 receptor previously known for its efficacy against RA. Monocyte macrophage cells synthesize two stimulatory cytokines IL-1β and IL-1α that act as initiators of the inflammatory signaling pathway therefore if any drug blocks their receptors it is hypothesized it will stop the production of CS. One of the studies centralized towards the use of anakinra showed a better flow of oxygen, prevention against mechanical ventilation, and provided information about the markers of blood inflammation without any signs of toxicity. One of the limitations associated with its use was its ability to generate an infection at the site of injection of the drug.

### VR23

Certain proteasome inhibitors harbor anti-inflammatory properties that may be an ideal strategy to target the CS. VR23 is a proteasomal inhibitor that reduces IL-6 levels in RA patients, secretion of TNF-α, tissue inflammation and decreases the neutrophil migration improving the acute lung injury induced by LPS (lipopolysaccharide) in mouse models.

### CYM-5442 and RP-002

Sphingosine-1-Phosphate (S1p) receptor is present in lymphocytes and endothelial cells in the lung tissues. Agonists of this receptor, CYM-5442, and RP-002 have shown...
### Table 1: List of potential anti-inflammatory drugs against Cytokine storm of COVID-19

| Name of drug                        | Target regions          | Mechanism of action                                                                 | Diseases are previously known for                                      | Side effects                                                                 | References |
|-------------------------------------|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------|
| Fedratinib                          | JAK2                    | Reduces cytokine load by inhibiting JAK2 required for TH17 cell differentiation       | Primary and secondary Myelofibrosis                                     | It can inhibit INF-γ required for curbing the virus activity                  | [25]       |
| Tocilizumab (TCZ)                   | IL-6                    | A recombinant monoclonal antibody designed to block both membrane-bound and soluble IL-6 receptors and their associated signaling pathways | Rheumatoid diseases and immunotherapy in cancer patients               | No toxicity is reported with its use                                         | [46–48]   |
| Emapalumab                          | INF-γ                   | IgG1 human monoclonal antibody has a high affinity towards INF-γ receptors and thus blocks it signaling | Multiple organ failure caused by hyper inflammation                     | Susceptibility to infection                                                  | [49, 50]  |
| Plerixafor                          | Antagonist of CXCR4     | Attenuation of TH17 cells and reduction of inflammatory cells into the airway prevents acute lung injuries | Stem cell transplantation                                               | No adverse effects have been reported so far                                 | [51, 52]  |
| Mycophenolate                       | IL-6, TNF-α, and IL-1β  | Inhibits the mRNA expression of various pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β | An immunosuppressive agent was used during a kidney transplant           | Diarrhea, urinary infections, and leukopenia                                | [53–56]   |
| Anakinra                            | The antagonist of IL-1 receptor | Blocks the receptors of IL-1β and IL-1α and further the signaling cascade for the cytokine storm production | Rheumatoid arthritis (RA)                                               | It may cause infection at the site of injection                              | [57–59]   |
| VR23                                | Proteasome inhibitor    | Reduces IL-6 levels, secretion of TNF-α, tissue inflammation, and neutrophil migration improving the acute lung injury induced by LPS | Rheumatoid arthritis (RA)                                               | Peripheral neuropathy                                                       | [60]       |
| CYM-5442 and RP-002                 | Sphingosine-1-Phosphate (S1p) receptor agonist | Reduces the cytokine production and inhibits the infiltration of innate immune cells. The cytokines that are inhibited involved IL-1α, IL-1β, IL-6, IL-10, MCP-1, TNF-α, and GM-CSF  | Influenza and other Coronavirus infections | No toxicity is associated with its use                                       | [61–64]   |
| Infliximab and Etanercept           | TNF-α                   | Infliximab is a monoclonal antibody that targets TNF-α and Etanercept is a protein that fuses with the TNF-α receptor causing its inactivation | Rheumatoid arthritis and other immune disorders                        | The risk of infections is associated with its use                           | [65–69]   |

*IL* interleukin, *TNF* tumor necrosis factor, *MCP* monocyte chemoattractant protein, *IFN* interferon, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *TH17* T helper cells, *JAK* janus kinase, *S1p* sphingosine-1-phosphate, *LPS* lipopolysaccharide, *CXCR4* C-X-C-chemokine receptor type 4, *TCZ* tocilizumab, *RA* Rheumatoid arthritis

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a considerable effect against severe influenza infection in the past. During the influenza infections of 2009, these agonists protected the mouse models from death by reducing cytokine production and by inhibiting the infiltration of innate immune cells [63]. The cytokines that were inhibited involved IL-1α, IL-1β, IL-6, IL-10, MCP-1, TNF-α, and GM-CSF. 80% protection to the mouse models was provided by these drugs; however, in combination with oseltamivir, mouse mortality reduced to 96% [64]. Interestingly, a patient of COVID-19 with pre-existing comorbidity of multiple sclerosis got successfully treated by this drug [62].

Consideration during drug testing

Antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent cellular cytotoxicity is a phenomenon where Fc receptors of effector cells can bind, interact, and kill the target antigenic substances coated with the antibodies. However, in some cases, ADE causes uptake of these antibody-bound antigen molecules into the effector cells promoting their enhanced replication and inflammation. Therefore, ADE should be an important aspect to be considered before proceeding for clinical trials of any drugs for therapeutic and vaccine development.

Inflammation by ADE effect

Liu et al. [76] have identified that the antiviral neutralizing antibodies targeted towards the spike protein of the virus instead of clearing the virus load have resulted in altered inflammatory responses resulting in severe lung injury. The mechanism behind the anti-Spike IgG antibodies (anti-S-IgG) mechanism is partially understood but it is hypothesized that the antibodies bind to Fc receptors present on alveolar macrophages leading to the production of pro-inflammatory cytokines such as MCP-1 and IL-8 in the lungs. They may also activate the classical complement pathway for mediating cell cytotoxicity [76]. But the major question that comes up is why only certain people face the adverse effects of ADCC while others can show a cleared viral load. This is perhaps because of the ADE that instead of reducing the viral infection promotes its replication and lung inflammation in a few patients. ADE allows anti-S-IgG antibodies bound to Fc receptors of macrophage cells to enter, replicate, and to produce pro-inflammatory cytokines [77–79]. Thus, this effect may support both viral replication and the inflammatory responses in the patient’s lungs. The other report says that they are two types of responses generated by the binding of anti-S-IgG antibodies to the Fc receptors. The primary response is less severe and the majority of people can combat it. This involves ACE2 shedding upon early viral replication leading to higher cytokine production and cellular injury through apoptosis/pyroptosis. Secondary response leads to the generation of an adaptive immune response where neutralizing antibodies (NAb) plays an essential part. About 80% of SARS-CoV infected patients had reported respiratory diseases after anti-IgG exposure [80]. FcR mediated cytotoxicity can thus be controlled by blocking these receptors [81, 82]. Different approaches to obstructing their interaction with IgG antibodies have been discussed in the next section.

Strategies in preventing the ADE effect

Three different approaches can be used in obstructing the interaction of the viral-NAb complex with Fc receptors on macrophages to prevent the ADE effect. Firstly, the use of antibodies or small molecule inhibitors that blocks the IgG-binding domain of Fc receptors can solve the purpose; Secondly, FCγRIIB may be used for inhibition of FCR activation. Various antibodies are available that have profound roles as immune suppressors [83, 84]. Thirdly, neonatal Fc receptor (FcRn) can be also be targeted for inhibition of FCR activation. These receptors are required for extending the half-life of the IgG antibody. Preventing the interaction with IgG and FcRn may be achieved by the use of antibodies or small molecules that causes the required blockage and thus, there will be a decrease in the circulating levels of the IgG [85]. Also, saturation in the binding ability of FcRn to IgG can be achieved through the supply of intravenous immunoglobulin (IVIG) [86]. We have mainly focused on blocking FCR for controlling ADCC, however, there is a possibility that cell uses the classical complement pathway for cellular damage. Thus, antibodies and molecules inhibiting c5 and c5a factors of the classical complement pathway can also be devised for reducing the severity of the infection and reversing the effects of ADCC [87].

Conclusion

This article highlights the inflammatory response of the host initiated upon the subsequent interaction of SARS-CoV-2 with human lung cells. The clinically approved anti-inflammatory drugs that might be useful in controlling the CS, provides new insights into what new strategies could be employed for further research in this field. Despite enormous efforts in producing the antiviral therapies, no specific clinical treatment exists so far and only partial information is known about the immunopathogenesis of SARS-CoV-2 infection suggesting the need to direct the future research in identifying the unexplored mechanisms. This study closes with a few research questions that need to be addressed for stepping closer towards achieving planetary health. Does our current knowledge...
of immunopathogenesis and inflammatory responses are sufficient enough in controlling the SARS-CoV-2 pandemic? Does inhibiting the JAK-STAT pathway could eliminate CS production? Are there any other alternative strategies that the host adopts to produce the CS if the JAK-STAT pathway is inhibited for TH17 cell differentiation? What is the true potential of anti-inflammatory drugs as a therapeutic intervention for targeting the pro-inflammatory cytokines and chemokines? Focusing research on these questions would shape our current understanding and knowledge on SARS-CoV-2 mediated inflammatory responses of the host and may provide suitable strategies in controlling the lung inflammation.

Future directions

The alarming rate of infection caused by COVID-19 in different countries of the world urges to look for immediate effective treatment and vaccine. Some poor and middle-income countries are facing problems in the diagnosis of infected patients. Higher IL-6 and IL-10 cytokines are important in deciding the prognosis of COVID-19 and hence, can be used as a marker for the diagnosis of infection. The use of glucocorticoids during the SARS-CoV outbreak in 2003 had been a great immunomodulatory therapy in providing a better oxygenation environment to the patient and in relieving the symptoms such as fever and pneumonia in providing a better oxygenation environment to the patient. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579:270–273

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Author contributions PA—Manuscript writing, acquisition of data, conception, and design of the study; MIH—Conception and design of the study, manuscript revision, final approval of version before submission.

Funding MIH thanks the Indian Council of Medical Research for funding the study (Grant No. BIC/12(01)/2015).

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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