

REVIEW ARTICLE

Cytokines Mediated Hyperinflammation in SARS-CoV2: An Overview

Liaqat Ali, Muhammad Faheem, Muhammad Tariq Navid, Sabba Mehmood, Wasim Sajjad

ABSTRACT

Hyperinflammation induced by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2) is a major cause of disease severity and mortality in infected patients. The immunopathogenesis of SARS-CoV2 infection is similar to the previous Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) and SARS-CoV coronavirus with severe inflammatory responses. Therefore, severity of this viral infection is not only associated with the virus but also due to host immune responses. Hyperinflammatory responses due to cytokine storm are a centerpiece of SARS-CoV2 pathogenesis with overwhelming consequences for the host. Virus infected monocyte derived macrophages produce cytokines and this contributes to damage of lymphoid tissue and limits the lymphocyte responses. Blocking the deadly cytokine storm and T lymphocyte stimulation is a vital defense for treating SARS-CoV2. Here, we will describe the role of hyperinflammation and the involvement of cytokines in severe SARS-CoV2 infection.

Key Words: Cytokine Storm, Hyperinflammation, MAS, SARS-CoV2.

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2) has emerged in December, 2019 in the city of Wuhan, China. Soon after, World Health Organization (WHO) has announced the SARS-CoV2 as a pandemic on March 11th, 2020.¹ This is a third outbreak that has originated due to coronaviruses during the last two decades. The identification of coronaviruses in non-human species (feline, canine, swine, bovine, equines, avian species etc.) posed a burden towards increase in outbreak chances. The earlier coronavirus outbreaks (SARS-CoV and MERS-CoV) have been originated from animal sources.² The current outbreak of SARS-CoV2 extends its threat to induce global health emergency and slumps world's economic growth by 3-6 % with a fall of \$90 billions revenue.³

The pathological mechanisms of inflammatory responses in SARS-CoV2 are not clear and still under

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investigation and regularly being updated. SARS-CoV2 is associated with hyperinflammation that drives multiorgan failure and lungs in particular. The route of viral transmission is same like other respiratory coronaviruses. In mild cases the incubation period is from 4-5 days and in symptomatic patients it is around 11.5 days after infection.⁴ The pathogenesis of novel SARS-CoV-2 infection resembles to the previous MERS-CoV and SARS-CoV infection with severe inflammatory responses.^{5,6} Therefore, severity of this viral infection is not only because of the virus but also due to host immune responses. Moreover, we focused on the role of inflammatory responses and cytokines involvement directly and indirectly in hyperinflammation in post SARS-CoV2 infection.

1. Genomic organization of SARS-CoV2

The coronaviruses are positive sense RNA viruses that belong to order Nidovirales, family *coronaviridae* and subfamily Orthocoronavirinae and categorized in four genera i.e. Alpha-, Beta-, Gamma- and Delta-coronavirus. SARS-CoV2 is an enveloped virus having a genome of approximately 30 kb that encodes four structural proteins viz Envelop protein (E), Spike protein (S), Membrane protein (M) and Nucleocapsid protein (N) (Figure 1).^{7,8}

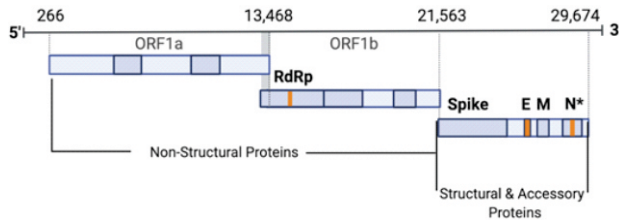


Fig 1: Genome organisation of SARS-CoV2. The genome is approximately 30 kb that encodes structural and non-structural proteins involved in viral replication and pathogenesis. (ORF: Open reading frame, RdRp: RNA dependent RNA polymerase, E: Envelope, M: Membrane N: Nucleocapsid): (Image generated: www.biorender.com)

Each of the protein plays an important role in the virus life as S-protein for host cell attachment, N-protein for nucleocapsid formation, M & E-proteins in viral assembly.⁹ The viral genome also expresses sixteen nonstructural proteins ranges from 1-16. The SARS-CoV-2 belongs to Beta-coronavirus genus and has 50-52 % and 79% similarities with MERS-CoV and SARS-CoV respectively.^{10,11}

The advanced genomic analysis identifies 380's amino acid substitution between SARS-CoV and SARS-CoV-2 viruses. This substitution along with other factors might be contributing to the functional and pathogenic divergence of novel corona virus.¹² The S-protein is immunological protein that contain receptor binding domain (RBD) that interacts with host cell ACE2 (Angiotensin Converting Enzyme 2) receptor and has epitopes recognized by T- and B-cells to induce neutralizing antibodies.¹³ ACE2 receptor is present on a variety of cells including pneumocytes, enterocytes, endothelial cells and cells of proximal tubules in kidney etc.¹⁴ RBD-ACE2 interaction mediates viral entry into the cell (Figure 2).

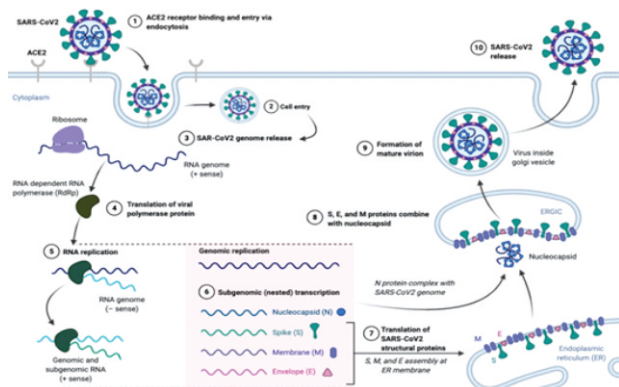


Fig 2: SARS-CoV2 infection and replication. (1) The virus binds to the cell surface receptor ACE2. (2) Entry of the virus to the cell mediated via endocytosis (3) The viral

genome is released in the cytoplasm of the cell. (4) RNA dependent RNA polymerase (RdRp) is translated from the positive sense RNA genome. (5,6) RdRp mediated transcription of genomic RNA to replicate the genome and sub-genomic RNA for translation of viral proteins. (7,8) Assembly of viral structural protein with nucleocapsid at the ER. (9) Formation of the mature virion in the golgi vesicle. (10) Release of the virus from cell surface. (Image generated: www.biorender.com)

This binding cleaves the S-protein into S1 and S2 parts through serine protease TMPRSS2 enzyme and thus allowing viral RNA to enter in cytoplasm.¹⁵

2. Hyperinflammation and pathophysiology

Hyperinflammation in SARS-CoV2 could be a driver of severity that is amenable to therapeutic targeting since retrospective data have shown that systemic inflammation is associated with adverse outcome as described by Mehta and colleagues.¹⁶ The corona virus infection is often narrated to hyperinflammation that drives multi-organ injury and lungs in particular. The pathophysiology and epidemiology of SARS-CoV2 are regularly being updated and the disease severity is not only restricted to the damage of epithelial cell but also to the hyperinflammatory responses that can target lungs and other injuries of human multiorgan, sepsis and mortality through cytokine storm⁴ (Table 1).¹⁷⁻³¹ Therefore, severity of this viral infection is not only because of the virus but also due to host immune responses.

Table 1: Possible genes in the pathways contributing hyperinflammation in SARS-CoV2

S. No	Gene	Cytogenic location	Function	References
1	JAK	1p31.3	Involved in interferon-alpha/beta and -gamma signal transduction pathways	17
2	STAT	2q32.2	Mediates cellular responses to interferons (IFNs), cytokine KITLG/SCF and other growth factors	18
3	GM-CSF	5q31	Stimulates the growth and differentiation of hematopoietic precursor cells from various lineages, including granulocytes, macrophages, eosinophils and erythrocytes	19

4	TNF	6p21.33	Associated with susceptibility to a number of compound disorders including Asthma, Dementia, Malaria, and Migraine etc	20
5	IFN γ	12q15	Rapid progression to AIDS, Aplastic anemia, response to therapy of hepatitis C	21
6	TLR4	9q33.1	Recognize pathogen-associated molecular patterns and mediate the production of cytokines necessary for the development of effective immunity	22
7	TLR7	Xp22.2	Involved in Pathogen-associated molecular patterns (PAMPs) that are expressed on infectious agents	22
8	TRAM	8q13.3	TRAM influences glycosylation and is stimulatory or required for the translocation of secretory proteins	23
9	NF-KB	10q24.32	Primary transcription factor found in all cell types. Role in the cellular responses to stimuli such as cytokines and stress	24
10	IRAK4	12q12	Important mediators in the signal transduction of Toll-like receptor and IL1R family members.	25
11	ACE2	Xp22.2	Involved in cleavage of angiotensin I into angiotensin 1-9, and angiotensin II into the vasodilator angiotensin 1-7. In addition, encoded protein is a functional receptor for the spike glycoprotein of the human coronaviruses	26
12	CD14	5q31.3	A surface antigen that is preferentially expressed on monocytes/macrophages	27
13	NLRP3	1q44	Interacts with the apoptosis-associated speck-like protein PYCARD/ASC and plays a role in the regulation of inflammation, immune response and apoptosis	28
14	CXCL-10	4q21.1	Encodes a chemokine of the CXC subfamily and ligand for the receptor CXCR3	29
15	IL-6	7p15.3	Encodes a cytokine that functions in inflammation and the maturation of B cells	30
16	IL-10	1q32.1	Cytokine produced primarily by monocytes and to a lesser extent by lymphocytes and is involved in the regulation of the JAK-STAT signaling pathway	31

Several mechanisms are involved in hyperactivation of macrophages during SARS-CoV2 infection. The pro-inflammatory macrophages differentiate through the enhancement of JAK (Janus kinase) and STAT (signal transducer and activator of transcription) pathways as described earlier.³² Activated macrophages releasing huge pro-inflammatory cytokines and contributing to the SARS-CoV2 cytokine storm. Stimulated natural killer (NK) cells and T lymphocytes promote the recruitment and activation of macrophages through the production of interleukin, tumour necrosis factor (TNF), interferon-(IFN), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-inducible protein (*IP*) and monocyte chemoattractant protein (MCP/CCL2) (Figure 3).

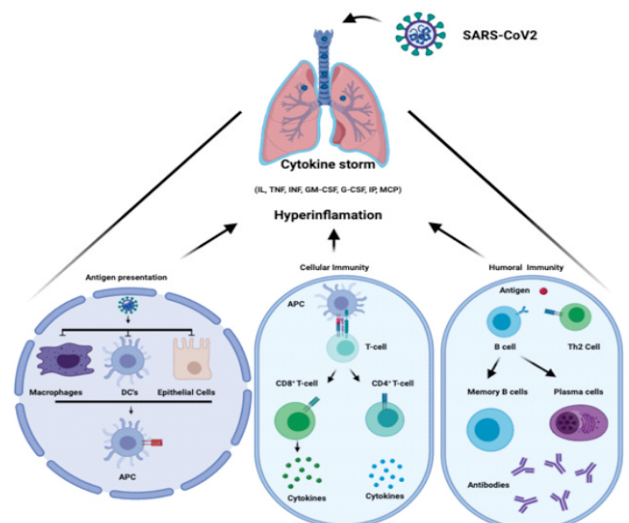


Fig 3: SARS-CoV2 infection in the lungs and cytokine storm. The viral infection leads to elicit both cellular immunity and humoral immunity. The antigen presenting cells (APC) take the virus and present the antigen to raise both innate and humoral immunity. The sensitization of the cells to release cytokines that multiply the signals. This signalling process cause intense cytokines production that can lead to cytokine storm and ultimately causing hyperinflammation (Image generated: www.biorender.com)

Acute respiratory distress syndrome (ARDS) observed in SARS-CoV2 infection, which is categorized by low level of oxygen and breathing difficulty. Although the massive cytokines release by the human immune system in response to the SARS-CoV2/or

other secondary infections can result the cause of death in 28 % cases.³³ The uncontrolled inflammation imposes leading to multiorgan damage failure, i.e.

hepatic, cardiac and renal systems. The depletion of T-lymphocytes in patients reflects huge recruitment to the inflamed tissues or mitigates inflammation due to use of steroids treatment.³² Recently, it is reported that T cells reduction from the secondary lymphoid tissues seen in infected patients but the exact mechanism is poorly understood.³⁴ Activation-induced cell death (AICD) is considered as the major cause of lymphopenia as T cells play a major role in viral suppression and clearance but in this regard IL-6 further functional characterization will be significant. Many research groups started clinical trials worldwide by combining IL-6 receptor and IL-1 β blockade in SARS-CoV2 patients that will shed light on severe disease pathophysiology and its associated inflammatory responses.

3. Defensive mechanism

3.1 Innate Immune response

After viral entry to the host cell, Pattern Recognition Receptors like TLR7 & TLR8, RIG-I-like, and NLR (all expressed by local alveolar macrophages and epithelial cells) do recognize SARS-CoV2. The ligand binding activates adaptor protein to enhance release of interferon regulatory factors (NF- κ B, and AP-1), resulted the production of antiviral interferon (Type I and III) and various types of chemokines.^{35,7} These chemokines enhance innate immune responses through recruitment of leukocytes, monocytes, NK cells, Dendritic cells (Figure 3). These cells are further linked with production of MIG, IP-10 and MCP-1, and recruit lymphocytes, which in return recognizes viral antigens, presented through dendritic cells. Recent investigation showed that immune and inflammatory responses by corona viruses equally infect pneumocytes and alveolar macrophages. *In-vitro* studies on SARS-CoV and SARS-CoV2 indicated that SARS-CoV induced better expression of interferon, while SARS-CoV2 was found less efficient in inducing many cytokines [11 cytokines by SARS-CoV while SARS-CoV2 mediates only 5 (IL-6, MCP1, CXCL1, CXCL5, and CXCL10/IP10)].³⁶

But, the results of *in-vivo* comparative transcriptional responses indicated SARS-CoV2 induces particular signatures even in reduced interferon responses.³⁷ Moreover, SARS-CoV2 induces significant mark on induction of various pro-inflammatory chemokines that makes SARS-CoV2 different from other coronaviruses. These changes

increased serum concentration in SARS-CoV2 infected patients due to replication within pulmonary tissue, escape from antiviral effects (interferon I & III), triggering of innate immune responses, activation and production of cytokines to recruit further adaptive immune responses.

3.2 Adaptive Immune Responses

The shifting over of adaptive immunity from innate immunity in SARS-CoV2 infection is poorly understood. T- lymphocytes, with CD4⁺ helping B-cells, uplift the production of specific antibodies to neutralize the virus and to the production of cytotoxic CD8⁺ to kill the infected cells (Figure 3). In COVID-19 patients, it was observed that 80% of the infiltrating cells are CD8⁺.³⁸ Inversely, a response of dysfunction to inhibit viral replication and infected cells elimination may result that possibly lead to cytokine storm and systemic consequences (intravascular coagulation). In SARS-CoV *in-vivo* model, Clay et al. (2012)³⁹ observed viral replication in lungs till 10th day post-infection; however, the severity of inflammation was at maximum till day 14th after viral clearance. These results suggested two phases of inflammatory responses; a viral dependent early phase and a viral independent but immuno-dependent later phase.

The second phase is thought to be due to inflammatory reactions followed by ACE2 inhibition or by an autoimmune factor owing to epitope spreading happened due to tissue destruction.⁴⁰ Some reports have suggested that DC-SIGN on the dendritic cells may act as trans-receptor for SARS-CoV, although the T- and B-cells, macrophages and dendritic cells don't express ACE2 on their surfaces. The function of T-cell infection is being speculated that it may be involved in lymphopenia which is observed in SARS-CoV, MERS-CoV and in SARS-CoV2 infected patients.⁴¹ The linkage of spike protein with CD26 and CD147 molecules activates T-cells and are involved in nonproductive T-cells infection might produce activation of AICD. The evidences showed that MERS-CoV induced T-cells apoptosis while in severe SARS-CoV2 infection; T-cells are functionally exhausted in patients.⁴²

4. Treatment and future perspectives

Hyperinflammatory responses causing macrophage activated syndrome (MAS), which is a lethal condition and related with high rates of mortality.

Therefore, timely detection and instant therapeutic intervention is critical to produce a quick response. The effectiveness of biologic agents or drugs in the treatment of MAS still remains unclear. Although it has been reported in few patients that the TNF α -inhibiting cytokine to be effective.⁴³ The clinicians mostly start treatment with intravenous methylprednisolone pulse therapy for three consecutive days. If the steroids response is not obvious in patients, initiated cyclosporine A (CsA) administration^{45,46}, which is associated with encephalopathy syndromic risk.⁴³ Unresponsive patients to the combination of CsA and steroids are treated with antithymocyte globulin (ATG) which suggested safer and depletes T lymphocyte through complement dependent cell lysis.⁴⁷

The activation of macrophages and release of cytokine play a key role in immunopathogenesis after SARS-CoV2 infection. Recent studies investigated consistent elevation of IL-6 in hospitalized patients.⁴⁸ Therefore, signal transduction of high level of IL-6 is significant to the CRS immunopathology that follows CAR T-cell therapies. Treatment with antibodies to IL-6R is considered the most effective to combat life-threatening conditions. A monoclonal antibody, Tocilizumab, targeting IL-6R used to treat rheumatic complications and also with CAR T-cell therapy as co-labeled by the FDA.⁴³ Around 16 clinical trials are in progress globally to determine the blocking efficacy of IL-6R in SARS-CoV2 infected patients. Type III interferon (IFN λ) targets epithelial and restricted pool of immune cells, which subsequently stimulate an antiviral effect without enhancing tissue inflammation.³² Neutrophil recruitment and associated activity might exacerbate SARS-CoV2 immunopathology.⁴⁹ Kaneko N and colleagues recently explained the partial durability of SARS-CoV2 antibody responses, which indicate that achieving herd immunity is difficult through natural viral infection.⁵⁰ In contrast to universal immune-suppression, specific inflammatory pathways could be targeted in SARS-CoV2 hyperinflammation. These approaches can be also combined with antivirals.

5. Conclusive remarks

The exact drivers of monocyte derived macrophage activation in SARS-CoV2 and the contribution to SARS-CoV2 disease pathophysiology remains to be

clarified. Virally infected monocyte derived macrophages produce cytokines and this contributes to damage of lymphoid tissue and this limits the lymphocyte response, exhausts and cannot control the macrophages. Hyperinflammation also reduce significantly in severe patients with broad interfering of cytokine signaling and several JAK inhibitors as in under trial testing. The upstream of individual cytokine production could be more effective to dampen the release of cytokine storm syndromes.

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