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Immuno-pathogenesis of nCOVID-19 and a possible host-directed therapy including anti-inflammatory and anti-viral prostaglandin (PG J_2) for effective treatment and reduction in the death toll

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ABSTRACT

Coronaviruses including severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, also known as 2019-nCoV especially in China) replicate and divide in host cells. During this they are partly hidden from the innate immune responses although inflammatory consequences of viral replication still occur. We propose that anti-inflammatory antiviral prostaglandins may not only restrict viral replication but also prevent inflammatory responses in the lungs and other vital organs that are known to be part of the immuno-pathogenesis of coronavirus disease-19 (COVID-19). The combination of anti-inflammatory antiviral prostaglandins with interferons may lead to the clearance of viruses inside growth-restricted infected cells. However, further experimental studies and clinical trials should be conducted to evaluate the safety and efficacy of these possible therapies.

Brief introduction about infectivity of SARS-CoV-2

SARS-CoV-2 spreads through direct person to person contact or via respiratory secretions (droplets from sneezing and coughing) and perhaps via contamination of fomites. Infective viral particles have been reported in respiratory secretions, stools and even sweat of patients [1,2]. After exposure to the host, the virus binds on the cells through its specific surface receptor the angiotensin-converting enzyme 2 (ACE2). There is an alternative receptor CD209L which has a much lower affinity for this virus [3]. ACE2 is highly expressed on the surface of epithelial cells of the trachea, bronchi, bronchial glands and alveoli inside the lungs [4]. Binding to ACE2 is critical for infection, and the infection then leads to production of many new viral particles which go on to infect other nearby or distant cells [5]. In addition to cells of the respiratory tract, ACE2 is also present on the surface of the tubular epithelial cells of the kidneys and renal tubules, endothelial cells of arteries and veins, mucosal cells of the intestines, cerebral neurons as well as on the surface of immune cells [1,6]. This allows SARS-CoV-2 to infect multiple organs.

Immuno-pathology of coronaviruses including 2019-nCoV

Initially most patients develop clear upper respiratory tract symptoms such as rhinorrhea, sore throat or sneezing, and less frequently intestinal symptoms such as diarrhea (approximately 20–25% of patients) [7]. During infection SARS-CoV-2 and other human pathogenic coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV can induce overexpression proinflammatory chemokines and cytokines. This contributes to the pathology of the disease, including the deterioration of respiratory linings, multiple organ failure and ultimate respiratory arrest [8,9]. The lung damage in SARS-CoV patients is associated with viral multiplication in bronchial and alveolar epithelial cells, as well being contributed to as being contributed to by macrophages via the synthesis and release of pro-inflammatory cytokines. However, the precise role of these direct and indirect mechanisms in lung injury remains controversial. Viral titers from nasopharyngeal aspirates decline after 10–15 days onset of symptoms, but this is not followed by lessening of clinical pathogenesis and alveolar damage, further reinforcing the host immune response's role in pathology during COVID-19 [10,11]. However, viral titers from nasopharyngeal aspirates do not always relate to total viral amounts, as high viral titers have been detected on autopsy in several organs including the intestine, lungs, brain and kidneys of SARS-CoV patients [2,12,13]. Also, infection of lymphocytes and macrophages is probably a key factor in SARS-CoV-induced pathogenesis [2]. SARS-CoV infection is associated with lymphopenia as well as atrophy of the spleen and lymphoid tissue as a result of directly infecting T cells [27]. That is the same in the case of murine coronavirus MHV-3 which also infects lymphocytes leading to

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lymphopaenia which consequently facilitates viral persistence as well as replication in the body [14]. SARS-CoV-infected lymphocytes results in systemic infection as these infected cells can transmit the virus to the distant organs [2]. A large number of infected and uninfected macrophages can accumulate in the lungs of patients who die of SARS-CoV infection [2,15,16]. Whilst infected macrophages have been detected *in vivo*, abortive infection of these cells has been demonstrated by SARS-CoV *in vitro* [17–19].

Immunopathology leading to severity and high death toll

The non-effective hyperactive and aberrant host immune responses induced by all three coronaviruses (MERS-CoV, SARS-CoV and SA SSARS-CoV-2 are the predominant cause of severe lung damage, leading to high mortality [20–22]. Many patients develop ARDS (acute respiratory distress syndrome) with typical pulmonary ground-glass changes on imaging.

These excessive and aberrant immune responses can be so harmful that even if patients survive in intensive care they face long term lung damage and fibrosis leading to functional disability and reduced quality of life [23,24]. The development and evaluation of drugs to specifically treat SARS-CoV-2 will take a long time, maybe several years, so attempts to reduce the immunopathology of COVID-19 may help in the short and long term. A range of FDA proved non-specific drugs (atorvastin, metformin, glitazones, sartans, and fibrates including nutrient supplements and biologics) [25–27], has already been suggested.

The pathophysiology of these highly virulent coronaviruses is not clearly understood. However, an elevation in proinflammatory cytokines such as IL-1β, IL-12, interferon-γ-inducible protein 10 (IP10), IFNγ, IL-6 and monocyte chemoattractant protein-1 (MCP1) in association with pulmonary inflammation and severe lung damage has been demonstrated in early studies on SARS patients [28]. The induction of high levels of proinflammatory cytokines such as IL-15, IL-17, TNFα and IFNγ also have been described MERS-CoV infection [29]. In the case of SARS-CoV-2 infection, high levels of IL-1β, IFNγ, IP10, and MCP1, which probably lead to the activation T-helper-1 (Th1) cell-based immune responses, has been noted [14]. Furthermore, high concentrations of granulocyte-colony stimulating factor (GCSF), IP10, MCP1, MIP-1α, and tumor necrosis factor α (TNFα) have been reported among ICU patients with SARS-CoV-2 infection [20–22,30,31]. These large amounts of cytokines have been called a cytokine storm that is associated to the severity of disease and death toll.

SARS-CoV inhibits the synthesis of type I interferons (IFNs) in infected immune cells and subsequently hinders the activation of the antiviral innate immune response. The synthesis of IFN is associated with phosphorylation and dimerization of IFN-regulatory factor 3 (IRF3). *In vitro* studies have shown that IRF3 does not activate in the SARS-CoV infected cells [17–19,32,33]. However, the expression of chemokines such as CC-chemokine ligand 2 (CCL2), CCL5, CCL8, CCL3 and CXC-chemokine ligand 10 (CXCL10) is upregulated in abortively infected macrophages and dendritic cells that probably contributes to the influx of further immune cells (monocytes and/or macrophages) that have been observed in the infected tissues [32,33]. Additionally, CCL2 and CXCL10 is found in high concentrations in the blood of SARS-CoV patients [28], and the over-production of neutrophil attractant CXCL8 (known as IL-8) also occurs among SARS patients [28,34,35]. Underlining the role of CXCL8 in the immune-pathogenesis, the severity of disease in the case of SARS-coronavirus is associated with the excessive elevation of neutrophil counts in the blood [36,37].

However, an increase in secretion of IL-4 and IL-10 (T-helper-2 (Th2) cytokines) has also been observed during SARS-CoV- 2 infection [28]. Th2 responses tend to suppress inflammation. Further studies are required to specifically describe the Th1 and Th2 base immune responses during SARS-CoV-2 infection as well as to clearly demonstrate its immuno-pathogenesis. The studies including autopsy and biopsy can help to understand the pathogenesis of disease leading to tissue damage organ failure.

Anti-inflammatory and antiviral therapy, and action of prostaglandin D2 Δ^{12}-PGJ_2

To date, there is no effective antiviral treatment for coronavirus infection. However, a combination of ritonavir and lopinavir has been used in a controlled study on SARS-CoV patients which gave some substantial clinical benefit with few clinical adverse effects [38]. A placebo-controlled trial has been proposed by Arabi et al., 2018, using interferon-1β together with ritonavir and lopinavir, against MERS infection in Saudi Arabia [39]. The protocol for this trial was recently defined by Arabi et al. [40]. Remdesivir has potency during the treatment of SARS-CoV and MERS-CoV infections [41,42].

Due to induction of high levels of cytokines during SARS-CoV infections [28,43] corticosteroids have been used to treat the severely ill patients. These may reduce the lung injury which occurs as a consequence of the high inflammatory response. In a cohort study on l41 laboratory-confirmed SARS-CoV-2 infected patients, corticosteroids were used to treat some non-ICU patients, as well as being applied in low-to-moderate doses to some severely ill patients having acute respiratory distress syndrome (ARDS) [43]. However, evidence from the SARS and MERS outbreaks indicates that corticosteroids did not prevent mortality, but rather its delayed the clearance of virus [44–46]. A recent commentary by Russell et al., 2020 reported that corticosteroids have no beneficial effects in reducing lung injury [47].

Anti-inflammatory cyclopentenone prostaglandins have also recently have been shown to have potent anti-viral action against several RNA viruses [38,42]. Cyclopentenone prostaglandins can inhibit viral replication by blocking the transcription and translation of viral RNA [48]. This type of inhibition is associated with the indication of heat shock protein-70 as well as inhibition of expression of nuclear factor κB (NF-κB) that is an inducible eukaryotic transcription factor responsible for the transcription of proinflammatory and viral genes [49]. Indomethacin, a cyclopentenone prostaglandin, has activity against human SARS-CoV [50]. The prostaglandin D2 (PGD2) as well as its derivative 15-deoxy-delta-prostaglandin J2 (15d-PGJ2) [51–56] can modulate inflammation by receptor-dependent DP1 and DP2 receptors on Th2 lymphocytes [57,58] as well as receptor-independent mechanisms [51,52,59,60]. PGD2 and 15d-PGJ2 can suppress inflammation including inhibition of nuclear factor-κB (NF-κB) by various mechanisms such as blockade of NF-κB nuclear binding, IκB kinase inhibition [51,52,59,60], and activation of peroxisome proliferatoractivated receptor-γ (PPAR-γ) [61]. The inhibition of secretion of IL-1β, IL-6, IL-12 and TNF-α and regulation of inducible nitric oxide synthase (iNOS) has been demonstrated in macrophages after the application of 15d-PGJ2 [62–64]. The dose-dependent anti-inflammatory effects of 15d-PGJ2 have been confirmed in animal models [65]. 15d-PGJ2 is more effective at inhibiting uric acid-induced acute inflammation than troglitazone, clearly demonstrating that 15d-PGJ2 may have the anti-inflammatory effects as well as inhibiting PPAR-γ [66]. Application of prostaglandin 15d-PGJ2 reduced morbidity and mortality in the mouse model of H1N1 influenza virus infection (that caused a previous pandemic). Prostaglandin 15d-PGJ2 reduced hypercytokinemia and immune-pathogenesis of in mice [67].

Δ^{12}-PGJ_2 prostaglandin J2 (a metabolite of prostaglandin D_2, (9-Deoxy-Δ^9, Δ^{12}-13,14-dihydro-prostaglandin D_2)) has antiviral activity against influenza A virus A/PR8/34 (H1N1) [68]. The antiviral action was associated with cytoprotective heat shock proteins induced by Δ^{12}-PGJ_2 in the infected cells [68,69]. This antiviral role of prostaglandin J_2 was previously demonstrated against Sendai Virus [70]. Δ^{12}-PGJ_2 as well as other cyPGs have been described as the key blocker of viral RNA transcription in-vitro leading to inhibition of replication of Herpes simplex virus [71,72]. cyPG can reduce the viral yield of vesicular stomatitis virus in infected cells by altering the synthesis and maturation of viral protein [73]. Δ^{12}-PGJ_2 is a potent inhibitor of influenza A

Table 1
Depicting the effective dose of PG J2 and Δ12 PG J2 form different in-vitro and in-vivo studies against different viruses.

Effective antiviral dose of PG J2 and Δ12 PG J2	Virus type	Cell cultures/Animal model	Reference
8–10 μg/ml	vesicular stomatitis virus	MA104 rhesus kidney cells	Pica et al. [73]
0.35–0.5 μg/ml	Herpes Simplex Virus type 2 (HSV-2)	Human embryonic fibroblasts (HEF)	Yamamoto et al. [72]
1.5–2 μg/ml	Human Immunodeficiency **Virus-1**(HIV-1)	CEM-SS cells (from human T lymphoid cell line)	Rozera et al. [48]
01–4 μg/ml	Sendai virus	African green monkey kidney cells (AGMK cells)	Santoro et al. [70]
10 μg/day/mouse (also reduce lung injury)	Influenza A/PR8/34 (H1N1)	BALB/c Mice (male)	Pica et al. [68]
(250 lg/kg/d) (also reduce lung injury)	Influenza A/PR8/34 (H1N1)	C57BL/6 Mice (female)	Cloutier et al. [67]

virus replication; a single treatment of a nontoxic concentration of Δ^{12}-PGJ_2 reduced virus yield above 95% within 72 h without affecting the synthesis of cellular DNA and RNA [68]. Intraperitoneal administration of Δ^{12}-PGJ_2 to the mice infected with PR8 influenza A was an effective treatment that decreased the viral load in the lung. Additionally, Δ^{12}-PGJ_2-treated mice were considered cured with no sign of disease in the following 3 months [68]. The effective dose of PG J2 and Δ12 PG J2 in from different in-vitro and in-vivo studies is shown in Table 1.

This evidence of direct antiviral effects of Δ^{12}-PGJ_2 suggest that it can be used to target SRAS-CoV-2 infection with minimal inflammation and immunopathology. Δ^{12}-PGJ_2 and other cyPGs may also be useful in combination with host-directed antiviral therapies such as lopinavir-ritonavir, ribavirin, remdesivir, interferon beta-1b, monoclonal antibodies, and anti-viral peptides [27].

Conclusions

Studies on SAR-CoV-2 infection indicates that its severity and death toll is associated with undesired non-specific immune responses which can also facilitate spread of virus other un-infected organs due. Therefore, it is important to regulate immune responses during infection. Prostaglandin J2 has anti-inflammatory as well as anti-viral activity. However, the application prostaglandin J2 needs further evaluation regarding safety and efficacy in humans.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110080.

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