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Review article

Cytokine Storm in COVID-19 Patients, their Impact on Organs and the Potential Treatment by QTY Code-Designed Detergent-Free Chemokine Receptors

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ABSTRACT

The novel coronavirus in not only causing respiratory problems, it may also damage the heart, kidneys, liver and other organs; in Wuhan 14 to 30% of COVID-19 patients have lost their kidney function and now require either dialysis or kidney transplants. The novel coronavirus gains entry into humans by targeting ACE2 receptor that found on lung cells, which destroy human lungs through cytokine storms, this leads to hyper-inflammation, forcing the immune cells to destroy healthy cells. This is why some COVID-19 patients need intensive care. The inflammatory chemicals released during COVID-19 infection cause the liver to produce proteins that defend the body from infections. However, these proteins can cause blood clotting, which can clog blood vessels in the heart and other organs; as a result, the organs are deprived from oxygen and nutrients which could ultimately lead to multi-organ failure and subsequent progression to acute lung injury, acute respiratory distress syndrome and often death. However, a novel protein modification tool called the QTY code, that are similar in their structure to antibodies, which could provide a solution to excess cytokines, these synthetic proteins can be injected into the body to blind the excess cytokines generated by the cytokine storm; this will eventually remove the excessive cytokines and inhibit the severe symptoms caused by the COVID-19 infection. In this review we will focuses on cytokine storm in COVID-19 patients, their impact on the organs and the potential treatment by QTY code-designed detergent-free chemokine receptors.

Keywords: COVID-19; Novel Coronavirus; ACE2 receptor; Cytokine Storm; Antibody-Like Fusion Protein.

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1 Introduction:

In December 2019, a cluster of pneumonia cases, caused by a newly identified β-coronavirus, occurred in Wuhan, China. However, there is no evidence so far that the origin of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was from the seafood market. Rather, bats are the natural reservoir of a wide variety of CoVs, including SARS-CoV-like and MERSCoV-like viruses [1-4]. This coronavirus was initially named as the 2019- novel coronavirus (2019-nCoV) on 12 January 2020 by World Health Organization (WHO). WHO officially named the disease as coronavirus disease 2019 (COVID-19), COVID-19 has spread throughout China and merged almost all over the globe. On 30 January 2020, WHO officially declared the COVID-19 epidemic as a public health emergency of international concern [5, 6].

The approximate incubation period of SARS-CoV-2(mean, 5.1 days; range, 4.5 to 5.8 days)[7]is in line with those of other known human coronaviruses, such as SARS (mean, 5 days; range between 2 to 14 days) [8] and MERS (mean, 5 to 7 days; range, 2 to 14 days) [9]Not all COVID-19 patients develop the same symptoms, but the immunological determinants of a poor prognosis are unknown. More than 50% of patients with Severe Acute Respiratory Syndrome Coronavirus 2 showed no signs of fever before hospitalization[10]. Strikingly, COVID-19 can be transmitted by asymptomatic patients, who show no fever, gastrointestinal or respiratory symptoms, and have normal chest computed tomography [11, 12] making it much more challenging to prevent the spread of COVID-19. Moreover, SARS-CoV-2 can remain viable and infectious in aerosols up to 7 days on surfaces [13]. A recent report from Shandong, China, disclosed that a subset of patients did not suffer from respiratory symptoms but had neurologic symptoms [14-16]; more young people infected with COVID-19 are dying of strokes are in their 30s – 40s while the average age of people who have strokes is 74; they do not show signs of severe infections or in some cases no sign at all. SARS-CoV-2 causes large vessel occlusions (LVOs) in some of COVID-19 patients; this can ultimately lead to death [17, 18]. How exactly the virus causes blood clots is still unclear. Some researchers believe it could be because of cytokine storm while others believe that SARS-CoV-2 disrupts the function of angiotensin converting enzyme 2 (ACE2) which causes imbalance in the renin-angiotensin-aldosterone system [19].

Although there are many vaccines candidates [20-26], but no effective treatment or vaccine have been developed so far[27-29]The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020, and raised the threat of the SARS-CoV-2 pandemic to the "very high" level on February 28, 2020.

Yao *et al.* provide direct evidence that the SARS-CoV-2 has recently developed mutations capable of significantly altering its pathogenicity. However, the novel coronavirus still gains entry into humans by targeting ACE2 receptor that found on lung cells, which destroy human lungs through cytokine storms, this leads to hyper-inflammation, forcing the immune cells to destroy healthy cells; we think this is why some COVID-19 patients need intensive care [30]. This review deals with cytokine storm in COVID-19 patients, their impact on the organs and the potential treatment by QTY Code-designed detergent-free chemokine receptors.

2 Cytokine storm and multi-organ failure:

Cytokine storm is considered to be one of the major causes of multiple-organ failure in COVID-19 infections. Excessive infiltration of the inflammatory cells like monocyte and neutrophil into lung tissue and thus lung injury, the damage to the lung happen through cytokine induced apoptosis of lung epithelial cells. IFN-αβ and IFN-γ induce inflammatory cell infiltration through two major mechanisms involving Fas–Fas ligand (FasL) or TRAIL–death receptor 5 (DR5) and cause the apoptosis of airway and alveolar epithelial cells. This will lead to alveolar edema and hypoxia and hence cause Acute Respiratory Distress Syndrome(ARDS)[31].In cytokine storm, the following cytokine levels are elevated IL-1b, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GMCSF, IFNg, TNFa, IP10, MCP1, MIP1A and MIP1B [32, 33]. which is associated with the severity of the disease [34], along with ARDS and cardiac injury in patient with underling heart problem [35].

2.1 Cardiac damage:

Patients with underling cardiovascular condition are vulnerable to cardiac injury and irregular heart rhythm, even more, some patients who have no recorded history of heart disease still develop cardiac injury when became infected with SARS-COV2 due to damage by the cytokine [36].Cytokines are also implicated in developing myocarditis and pericarditis in covid19 patients. That is why treatment with cytokine inhibitor like IL-6-targeting therapies in these patients has showing promising result [37, 38]. In a retrospective cohort study done by Zhou *et al.* in Wuhan, China involving 191 COVID19 patients. Increased high-sensitivity cardiac troponin I during hospital admission was noticed in more than half of those who died [39]. Furthermore it was found that d-dimer rise above 1 μg/mL is associated with fatal outcome. Systemic pro-inflammatory cytokine responses are thought to be mediators of atherosclerosis leading to plaque rupture through local inflammation, induction of procoagulant factors, and haemodynamic changes, which eventually lead to ischaemia and thrombosis. In addition, angiotensin converting enzyme 2, the receptor for SARS-CoV-2, which is expressed on myocytes and vascular endothelial cells could play role in myocardial injury [40-42].

2.2 Acute Respiratory Distress Syndrome (ARDS):

The pneumonia associated with COVID-19 could be complicated by acute respiratory disease syndrome which is confirmed by the appearance of bilateral glass appearance on the computer tomography [43]. The pathophysiology of covid19 associated ARDS has similarity to that of severe community-acquired pneumonia induced by other viruses [44]. Activation of coagulation pathways in cytokine storm syndrome will lead to progressive lung injury. Furthermore, thrombin plays vital role in promoting clot formation and preventing bleeding but another significant role is the augmentation of inflammation via proteinase-activated receptors (PARs), particularly PAR-1, which is why PAR-1 antagonists is a promising mode of treatment in alleviating the lung damage associated with cytokine storm. Thrombin generation is regulated by factors, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system, which all became impaired during inflammation leading to the formation of micro thrombosis and acute lung injury [45, 46].

2.3 Renal:

The incidence of acute kidney injury in COVID-19 patients was estimated to be up to 5%. It is more common in intensive care setting and could be considered as a poor prognostic factor for survival [47]. The inflammatory response associated with cytokine storm will lead to hypo perfusion injury to the renal tubules coupled with increased vascular permeability and cardiomyopathy, which may lead to developing cardio renal syndrome type 1, a condition characterized by pleural effusions, edema, intravascular fluid depletion and hypotension [48]. In addition, direct cytopathic damage caused by SARS-COV-2 are thought to be one of the underlying mechanisms of renal damage associated with COVID-19 [49, 50].

2.4 Liver:

It was thought that COVID-19 causes direct liver injury through viral hepatitis, which is accompanied by the rise in bilirubin and aminotransferase levels in covid19 patients [51, 52], yet studies suggested that clinical liver injury is uncommon on the course of the disease. So it is possible that elevated liver enzyme may not be from the liver alone and confounding factors like myositis could be the cause behind this rise [53].

2.5 Central nervous system:

In a retrospective, observational case series, involving 214 patients with COVID-19, neurological manifestation like headache, ataxia and seizure were noticed in 36.4 % of them. These manifestations were more common in patients with severe form of the disease. These symptoms could be due to ACE receptor involvement, in addition to elevated proinflammatory cytokines in serum associated with cytokine storm, which may lead neurological symptoms due to skeletal muscle damage [54, 55].

3 Immune Dysfunction:

Peripheral CD4 and CD8 T cells showed reduction and hyperactivation in a severe patient. High concentrations of proinflammatory CD4 T cells and cytotoxic granules CD8 T cells were also reported, suggesting antiviral immune responses and overactivation of T cells [56]. Furthermore, numerous studies have described that lymphopenia is a common feature of COVID-19 [36, 57], suggestive of a dynamic factor accounting for severity and mortality.

4 Inhibition of cytokine storm by QTY code-designed detergent-free chemokine receptors:

Cytokine storm is the leading side effect during cellular immunotherapy that is potentially life-threatening. It can also be triggered by viral infections such COVID-19 infections. COVID-19 triggers cytokine storm in many stages of its pathological course that causes lung fibrosis, acute respiratory distress syndrome, and eventually leads to multi-organ failure [36, 56, 58]. To alleviate the symptoms and treat the disease, it's vital to efficient removal of excessive cytokines efficiently and rapidly [35]. However, not all patients with COVID-19 develop the same symptoms, but the immunological determinants of a poor prognosis are unknown. Yang, Y *et al.* followed a cohort of 53 clinically moderate and severe patients; they conducted a multiplex

screen for 48 cytokines and correlated these results with lab tests, clinical characteristics and viral loads. They found a marked increase of 14 cytokines in patients with COVID-19 compared with healthy controls. Continuously high levels of three of these cytokines (CXCL10, CCL7 and IL-1 receptor antagonist) were associated with increased viral load, loss of lung function, lung injury and a fatal outcome [59].

Zhang *et al.* reported a novel protein modification tool called the QTY code, through which hydrophobic amino acids Leucine, Isoleucine, Valine and Phenylalanine are replaced by Glutamine (Q), Threonine (T) and Tyrosine (Y). Therefore, the functional detergent-free equivalents of membrane proteins can be designed. The QTY code-designed detergent-free chemokine receptors may be useful in many applications such as infectious diseases, designing biologics to treat cancer and autoimmune [60].When the QTY designed water-soluble Fc-receptors bind to excessive cytokines, they inhibit cytokine storm with target cells, therefore, reducing organs failure and toxicity. The QTY code allows membrane proteins to be designed through simple, specific amino acid substitutions. The QTY code is robust and direct; it is the simplest tool to carry out membrane protein design without sophisticated computer algorithms. Thus it can be used broadly [60].

Hao *et al.* reported the application of the QTY code on six variants of cytokine receptors, including interleukin receptors IL4αR and IL10αR, chemokine receptors CCR9 and CXCR2, as well as interferon receptors IFNγR1 and IFNλR1. QTY variant cytokine receptors exhibit physiological properties similar to those of native receptors without the presence of hydrophobic segments. The receptors were fused to the Fc region of IgG protein to form an antibody-like structure. Cytokine receptor-Fc fusion proteins potentially serve as an antibody-like decoy to dampen the excessive cytokine levels associated with CRS and COVID-19 infection [61]. **Figure 1** shows a schematic illustration of these cytokine receptor-Fc complexes for the 6 QTY receptor variants. The structural illustrations of corresponding cytokine receptors were obtained through Protein Data Bank [62-66] where applicable or from a homology model (CXCR2) [67].

5 Advantages and limitations of cytokine storm inhibition by QTY code-designed detergent-free chemokine receptors:

Cytokine receptor-Fc fusion proteins potentially serve as an antibody-like decoy to dampen the excessive cytokine levels associated with CRS and COVID-19 infection. Hao *et al.* specifically designed the QTY receptor variants to fuse with the Fc region of IgG protein in order to acquire an antibody-like structure. The primary benefit of Fc fusion is to significantly enhance the half-life of the fused protein in human plasma. It can also improve the safety of the fused proteins due to reduced immunogenicity while synergistic therapeutic effect from both fusion parts is achievable [68]. QTY receptors are capable of binding to their respective ligands with high affinity close to isolated native receptors on solution-based assays [61]. Another advantage, The Fc region can be easily exchanged in future designs. Although there have been many Fc-fusion proteins developed (20 Fc-fusion proteins) for various applications, they are water-soluble proteins in the native state [69, 70]. QTY code designed Fc-fusion

receptors, especially chemokine receptors CCR9 and CXCR2, provide a novel platform for further design of other types of fusion membrane receptors for therapeutic and diagnostic applications [61]. The limitation of QTY code-designed detergent-free chemokine receptors is had been tested in mice only while the human clinical trials had been startedon April 2020[61].

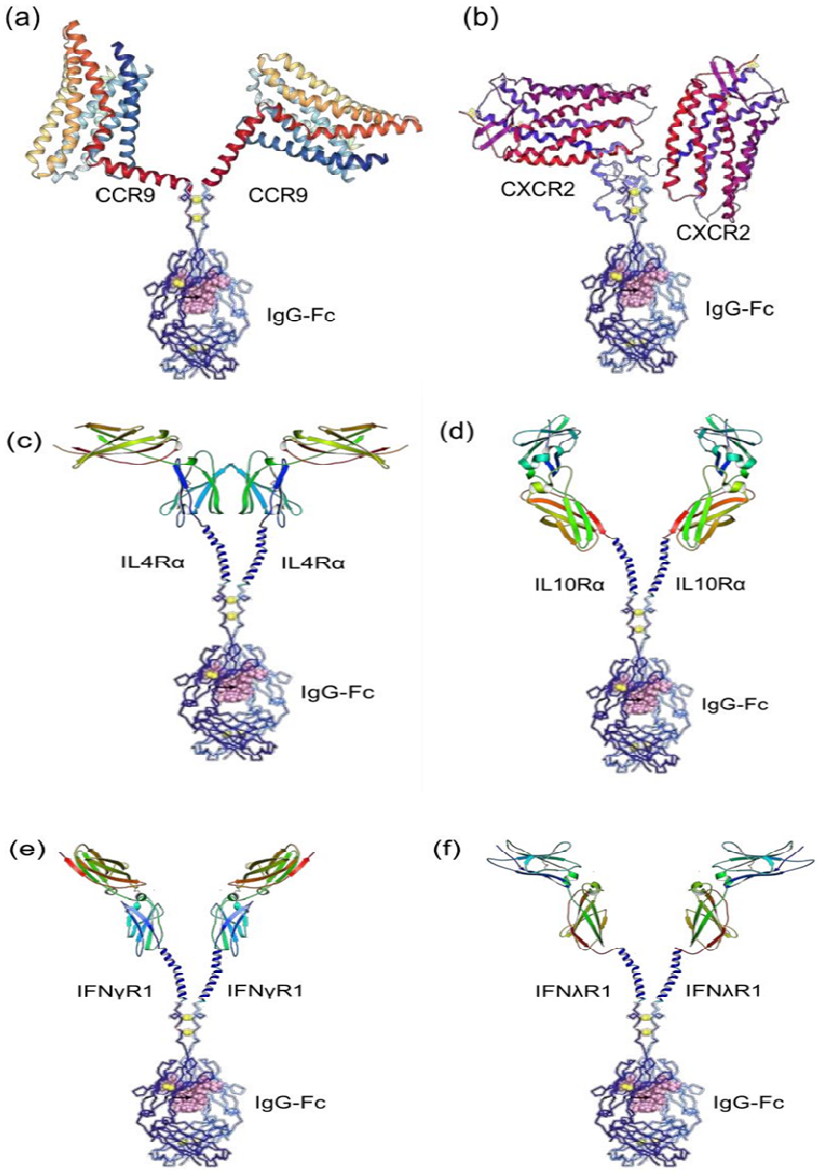

Figure 1: illustration for Fc fused QTY variant cytokine receptors with antibody-like structure: (a) CCR9QTY-Fc; (b) CXCR2QTY-Fc; (c) IL4RαQTY-Fc; (d) IL10RαQTY-Fc; (e) IFNγR1QTY-Fc; (f) IFNλR1QTY-Fc.

6 Conclusion:

Cytokine storm is the leading side effect during cellular immunotherapy that is potentially life-threatening. It can also be triggered by viral infections such COVID-19 infections. Importantly, COVID-19 has many consequences which induced by cytokine storm in many stages of its pathological course that causes lung fibrosis, acute respiratory distress syndrome, and eventually leads to multi-organ failure and may also leads to death. To alleviate the symptoms and treat the disease, it's vital to inhibit cytokine storm efficiently and rapidly. Nevertheless, not all patients with COVID-19 develop the same symptoms. However, a novel protein modification tool called the QTY code, that are similar in their structure to antibodies, which could provide a solution to excess cytokines, these synthetic proteins can be injected into the body to blind the excess cytokines generated by the cytokine storm; this will eventually remove the excessive cytokines and inhibit the severe symptoms caused by the COVID-19 infection.

Declarations

Competing interests:

The authors declare that they have no competing interests.

Authors' contributions:

All authors wrote and revised the paper. All authors read and approved the final manuscript.

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