COVID 19: AN OVERVIEW OF PATHOGENESIS, CYTOKINE STORM AND INTERFERONS AS A POTENTIAL DRUG THERAPY

Microbiology

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ABSTRACT

Novel Coronavirus (SARS-CoV-2) causing Coronavirus disease (COVID-19) has become a pandemic and has not been previously identified in humans. Transmission among humans occurs through respiratory droplets of infected individual. Patients infected with SARS-CoV-2 undergo acute respiratory distress because of Cytokine storm which serve as the major cause of morbidity and mortality in affected individuals. Cytokines are defined as non-structural proteins which are small with low molecular weight and have a greater regulatory influence in inflammation and immunity. They are considered as the intercellular messenger in the immune system.

Therefore, this article provides a glimpse of advancements made in the area of SARS-CoV-2 infection where Cytokines may be a useful biomarker for both diagnostic and prognostic purpose and also as a therapeutic agent in targeting certain cytokines responsible for Acute Respiratory Distress Syndrome (ARDS) in SARS-CoV-2 infected patients.

KEYWORDS

SARS-CoV-2, Cytokine. Cytokine storm syndrome, ARDS

INTRODUCTION:

COVID-19 caused by the Novel Coronavirus is a potentially fatal disease which led to an unprecedented global pandemic [1]. Cytokine storm syndrome was believed to be the major pathogenesis behind the SARS-CoV-2 induced pneumonia [7]. Few clinical investigations showed an up regulation of Cytokines and Interferons in patients affected with SARS-CoV-2 [3]. There is no proven effective drug therapy nor vaccines for SARS-CoV-2 till date. Thus, it is crucial to recognise the approved therapies that could reduce the mortality associated with COVID-19 due to hyperinflammatory state of the lung. Hence, this article evaluates several options that is needed to control the mortality of SARS-CoV-2.

IMMUNOPATHOGENESIS OF PATIENTS INFECTED WITH COVID-19:

Coronaviruses are enveloped virus with a positive sense single stranded RNA genome and a nucleocapsid of helical symmetry [4]. SARS-CoV-2 is a major public health concern infecting humans

especially elders and those who are immunocompromised. COVID-19 infected patients transmits the virus through droplets of saliva or discharge from the nose [5]. When the infected droplets comes in contact with a healthy person mucosal membrane pathogenesis begins. Generally, nasal cavity is the most common site of entry for COVID-19. The viral load of COVID-19 mostly determines the severity of the disease.

Coronavirus, uses a Spike-protein to infect a host cell by binding to the membrane of the cell. COVID-19 binds with Angiotensin Converting Enzyme 2(ACE2) receptors in humans for producing infections [6]. After binding with the ACE 2 receptors this virus gets pinched inside the host cell. On subsequent entry into the nucleus of the host cell the genetic material of COVID-19 gets replicated. ACE 2 receptor was believed to be a functional receptor for SARS-CoV-2 [7,8]. ACE 2 receptors was expressed in various organs like lung, heart, ileum, kidney and bladder. Whereas in lung ACE 2 receptor was predominantly found on lung epithelial cells [8,9].

FIGURE 1: Pathogenesis and phases of sars-cov-2

The symptoms of patients infected with COVID-19 vary from mild to severe acute respiratory failure with multiple organ dysfunction. As an antiviral mechanism, Antigen Presenting Cells(APC) are involved in the presentation of viral antigenic peptides in complexed with MHC(Major Histocompatibility Complex) Class I and Class II

FIGURE 2: Replication of sars-cov-2 inside the host

molecules to CD8 and CD4 T cells(5). During ant viral infection, DC's (Dendritic Cells) play a very important role as an APC. DC's are the linkage between Innate and Adaptive Immunity. DC's are predominantly found in the respiratory tract and take a role in any inflammatory response [10].

In a previous study, histopathological examination of lung from an infected person showed prominent desquamation of pneumocytes and formation of hyaline membrane indicating signs of ARDS(6). The examination finding also revealed interstitial mononuclear patchy inflammatory infiltrates dominated specifically by lymphocytes. These pathological changes may provide new insights into the pathogenesis of pneumonia induced by SARS-CoV-2 [11,12].

CTOKINE STORM SYNDROME IN PATIENTS INFECTED WITH SARS-CoV-2:

The term "Cytokine storm" is considered when the cytokines are produced in excess leading to Hypercytokinemia which occurs as a result of overreaction by the human body's immune system in response to an intruder [13]. During ARDS, the immune effector cells have been shown to release huge amounts of chemokines and proinflammatory cytokines, which result in fatal unconfined or uncontrolled systemic inflammatory response. As previous data suggest, pandemics caused by Coronavirus such as MERS-CoV(Middle East Respiratory Syndrome-related Coronavirus) and SARS-CoV(Severe Acute Respiratory Syndrome- related Coronavirus) caused massive release of proinflammatory cytokines such as (Interferon-alpha, Interferon-gamma, Interleukin-6, Interleukin-12, Interleukin-18, Tumor necrosis factor-alpha and Tumor growth factor-beta) and chemokines such as (CXCL10 and CCL2) which are associated with hyperinflammation of the lung and extensive lung damage [11].

To further highlight, in patients with SARS-CoV-2 infection there is also an increased secretion of Th2-immune oriented cytokines such as IL-4 and IL-10, which plays a major role in suppressing inflammation.

FIGURE 3: Stepwise representation of cytokine storm syndrome

CYTOKINES AS DIAGNOSTIC BIOMARKER IN COVID-19 INFECTED PATIENTS:

Cytokines are triggered as a result of influencing immunity in a host for a particular infection. But in hypercytokinemia where the cytokines are released in excess to suppress inflammation results in fatal outcome. These elevated cytokines/chemokines play a different role in response to every pathogenic infections [8]. Interferons that are considered to be an antiviral cytokines when raised in higher levels are "good" to enhance immunity in the host and also help in eliminating the pathogen. Whereas, proinflammatory cytokines such as IL-6 when secreted in higher levels trigger multiple cytokines leading to excessive damage to the tissues and organ failure. A study conducted by Yingxia Liu, measured 48 key cytokines/chemokines in blood plasma of a 12 COVID-19 positive patients using a cytokine screening panel which showed a significant increase of 38 cytokines/chemokines in blood plasma of patients infected with SARS-CoV-2. This study also compared the levels of cytokines with healthy individuals and patients affected with bacterial pneumonia where it was found to be lower in the control groups [12]. There is also indication of persistent elevation of plasma cytokines/chemokines even at the later stage of COVID-19 patients. Through these results we get a better picture of the pathological and immunological response to COVID-19. We also understand that the cytokine modulators may play a keyrole in therapeutic management of COVID-19.

INTERFERONS-AS A POTENTIAL DRUG THERAPY FOR COVID-19PATIENTS:

Interferons are a group of signalling proteins released by host cells in response to the presence of several viruses. They also activate immune cells such as natural killer cells and macrophages. Because of the anti-viral or immunomodulatory properties exhibited by these interferons they were used in some viral conditions such as chronic hepatitis also in non-viral diseases including leukemia,multiple sclerosis, multiple

myeloma and chronic granulomatous disease [11,12]. Previous data suggested that patients infected with MERS (Middle East Respiratory Syndrome), SARS (Severe Acute Respiratory Syndrome), Human coronavirus 229 E and Avian infectious bronchitis virus showed greater response to Interferon treatment. A combination therapy of Ritonavir and Interferon alpha 2a or Interferon alpha 2b has significantly helped in survival of patients infected with MERS [11].

Therefore, it is an utmost need and urge to test the safety and efficiency of recombinant Interferons in humans to treat the patients infected with SARS-CoV-2 alone or in combination with other antiviral drugs.

CONCLUSION:

Coronavirus is one of the most serious viral diseases of the decade, infecting humans, originated from the city of Wuhan, China, by the end of December 2019 has left the world shaken up. The emergence and outbreak caused by SARS-CoV-2 is determined by the disruption of the host immune system by the virus. Henceforth, early diagnosis is the key for prompt management of COVID-19. Serological and molecular assays together will further strengthen the diagnosis of SARS-CoV-2 and newer approved therapeutic inventions may help in treatment of patients affected with SARS-CoV-2.

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