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Review Article

The SARS-CoV-2 and Human Immune System

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Abstract

The genetic make up of the COVID-19, critical patients in ICUs was compared with the genomes of healthy person to identify any genetic differences. It was found that few genes like, TYK2 are seen in such patients which makes the immune cells more annoyed resulting in more inflammatory response. But if the gene is faulty, the patients hyper immune response can go into overdrive, putting him at risk of pulmonary injury and cytokine storm (CS). This analysis highlights the unique characteristics of patients with COVID-19 disease that genomic and laboratory parameters present an imbalance in cytokine storm players (pro inflammatory stage, cell death, multi-organ tissue destruction, and electrolyte imbalance).

Key words: COVID-19, Genes, Immune system, Overrides, SARS-Cov-2, TYK2, Critical stages, ICUs.

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Introduction

A study conducted on 2,200 patients suffering from COVID-19, and admitted in ICUs. It showed that specific genes responsible for faulty uncontrolled hyper-immune response, leading the patients at risk of pulmonary injury. These genes make these patients more susceptible to severe COVID-19 symptoms. These genes make the patients more vulnerable to the effects of extreme COVID-19.

The study shows that basically, the human immune system goes wrong, which demands to identify alternative therapies or reprocess the existing drugs to treat COVID-19 alongside other therapies. There will most likely be a genetic component associated with disease severity. However, the degree to which the impact is seen is yet to be determined.[1-2]

New treatment modalities like vaccines are being developed, vaccines will continue to be needed, says Dr Kenneth Baillie, a physician at the Royal Infirmary in Edinburgh, who led the Genomic project. "Vaccines should drastically reduce the number of cases of COVID-19, but doctors are likely to continue treating the disease for a number of years in intensive care around the world, so there is an urgent need to treat the disease in intensive care". [3]

In COVID-19 Patients, Angry' cells of immune system are faulty

The researchers analyzed the DNA, of >200 critically ill patients admitted to intensive care units of corona hospitals in United Kingdom and found that all have problem in their immune system. To combat this SARS-CoV-2 viral infection, they tested each person's genes, which contain the knowledge for each natural process and found them at fault. A gene called DPP9, which plays a role in inflammation, and a gene called OAS, which helps stop the virus from producing copies of it, has also shown genetic variations.[3-4]

The COVID-19 interferes the interferon synthesis.

When the virus enters human cells, it deregulates its ability to make own proteins like IF. When interferon is not formed, the accompanying cell has no idea what is happening to it because interferon helps human cells to develop anti-virus informing machinery. The coronavirus decodes "MDA5: and "IRF3" IFNAR2 in cell codes and the nuclei of human cells cannot make messenger RNA (mRNAs) that can tell ribosomes to make an interferon and thus weaken the human immune system.[5]

In intensive care patients, variations in a gene called IFNAR2 have also been reported. IFNAR2 is associa-

ted with a strong anti-viral molecule called interferon, which, as soon as an infection is detected, helps kick-start the immune system. It is suspected that producing too little interferon will give the virus an early advantage, enabling it to replicate rapidly, leading to more serious disease.[3-5]

In COVID-19 cases, two other recent studies published in the journal 'Science' have also involved interferon through both genetic mutations and an autoimmune condition that inhibits its development.[3] Interferon may be offered as a therapy, but one clinical trial by the World Health Organization concluded that it did not benefit very sick patients. Prof Casanova, however, said the timing was significant.[5-8]

The genes of the patient with COVID-19 hold answers as to why those individuals get critically ill, the SARS-CoV-2 over rides the genes which control the immune system of the humans, TYK2, DPP9, and IFNAR2 went down regulated in patients suffering from critical stages in ICUs. There is cytokine storm and patients go in critical stages and prognosis is poor.[3]

There is marked cytokine storm which frequently increase the lung tissue damage during respiratory viral infection, most likely due to fault in their immune system. The virus inhibits the production of interferon in human cells in three ways.[3-5,8]

1. First paralyzes the protein transcription system.
    a. Degradation of transnational pathway.
    b. These viruses inactivate RIG1 and MDA5 in human cells, and when these codes are not developed, they cannot form IRF3 and thus transcription does not occur because the same IRF3 transcription proceeds.
    c. When there is no transcription, there is no trans-lation and mRNA is not formed and messaging RNA is not formed, then ribosomes ribosomes do not know whether interferon is formed or not.
    d. Non-structural protein NSP16 of the corona virus, combines with the U1 and U2 of the nucleus to inactivate the splicesosomes and thus prevent the messenger RNA from forming.
2. The second method is the failure of the translation method is degradation of translational pathway;
3. It happens that even if transcription occurs and mRNA A is formed, the NSP16 of the corona virus does not allow it to combine with ribosomes, and when the protein-making factory does not know what to prepare, then how will human cells interferon be made
4. Third method is paralysis of signal recognition system due to failure of signal recognition particles) SRP9 and SRP8. In this method, even if some enzymes are formed, they cannot be excreted out of the cell because the SRPs become useless.
    a. This is called failure of the protein trafficking system or failure of secretion.
    b. A research paper shows how the SARS-COV-2 disrupts mRNA splicing, protein translation, and protein trafficking in our cells. This leads to reduced production of interferon, which in turn, causes reduced viral defense by the host cells.
    c. SARS-CoV-2 not only lowers interferon but also many other functional proteins that weaken the human immune system. This study also suggests the development of drugs that can inhibit the virus's action, such as interferon, ivermectin, may be effective in treating the disease.

A- Deterioration of Immune system in COVID19

As we have stated above, there are four possible causes, which appear after the attack of SARS-COV-2 in humans. When the corona virus attacks, there is hyper inflammation throughout the body and in this case the inflammatory markers are increased. Hyper-inflammatory syndrome occurs in patients with extreme COVID-19, affecting morbidity and mortality. This research investigates a particular phenotype of hyper inflammation associated with COVID-19 (COV-HI) and its associations with respiratory support escalation and survival. To assess this condition, the physicians must correlate with laboratory findings. The laboratory markers in such conditions are raised like serum Ferritin, CRP, Interleukin -6 (IL6), Triglycerides and Albumin. In critical conditions, these markers are raised three times of their normal range (Table 1) [9-11]

The existence of a high-risk patient phenotype is evidenced by the correlation with elevated hyper-inflammatory mediator, accelerated respiratory assistance, and survival in people with COVID-19. The identification of these phenotypes with COV-HI can be useful in stratifying patient classes, their survival targeting new treatment.[12]

B- Immune system Dysregulation in COVID-19

Immune system dysregulation can lead to inappropriate local and systemic immune responses, resulting in the rapid spread of SAR-CoV-2, leading to severe COVID-19 disease. Therefore, recognizing the differences in different hosts' immune responses and improving the disorder of the immune system should always be part of research and treatment protocols.[13]

The following markers are damaged when both the human immune system is infected with SARS-CoV.9 Over activity of innate immune system o, results in increased neutrophils count raised monocytes. Adaptive immune system dysfunction results in decreased lymphocytes.[10]

C- Tissue damage of human system in sever cases of COVID-19

The highest levels of coronavirus load have been seen in the patient's respiratory tract, but low concentrations have also been found in the kidneys, liver, heart, brain and blood. These results suggest a possible SARS-CoV-2 organ tropism that could affect the progression of the disease, possibly leading to aggravation of the underlying conditions. When coronavirus attacks, there is tissue damage throughout the body and in this case the inflammatory markers are increased.[9,14]

It is useful, for the assessment of nutritional status and liver dysfunction by assessing the serum albumin levels. To assess the individual cell damage of tissue destruction, the level of LDH is estimated, the high level shows sever, shock, hypoxia, due to pulmonary injury. Serum procalcitonin is useful for the diagnosis of bacteremia and septicemia when develop sever form of the disease. The high level of CRP, is useful for the detection of systemic inflammatory process, it also indicates the severity of viremia and sepsis, and association of the patient's prognosis. Same is the assessment of serum ferritin level, shows patient status of coagulation system. The enzymes increased are cardiac troponin I and hepatic enzymes ALT / AST. These findings must be correlated with the mode of selection of treatment in these situations (Table 1-2). [9-15]

Endothelial Damage in COVID-19

The SARS-CoV-2 attacks the endothelium of the blood vessels and causes damage of endothelial cells, which results in release of many chemical mediators and enzymes like LDH (Generalized cell death) and Troponin I. (Damage of heart tissues).[16-17]

The critical role of immunological hyper-response characterized by widespread endothelial disruption, complement-induced blood clotting and systemic microangiopathy in disease exacerbation is highlighted by insights into the pathogenic mechanisms underlying SARS-CoV-2 infection and COVID-19 progression. Such insights can help identify new or existing therapeutic interventions.[17-18]

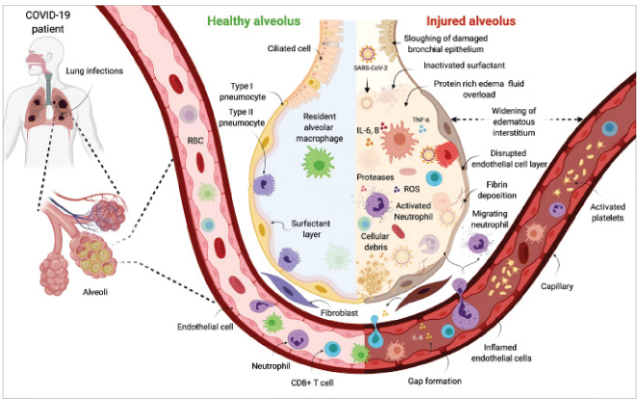

Figure. 1 *Mechanism of Action of SARS-CoV-2.*[17]

D- Pre-renal and renal damage (pretension overload and renal damage)

When the corona virus attacks, there is pre renal overload and renal damage and in this case the following markers become abnormal. The electrolytes like Potassium (K^+), Calcium (Ca^{++}), Chloride (Cl^-) may become abnormal but may be normal in some cases. Blood Urea, Serum creatinine and BUN are high considerably.[9]

Dr. Vanessa Sancho-Shimizu, an Imperial College London geneticist, said the genetic findings offered an unparalleled insight into the biology of the disease.[3-9] But there are still some mysteries in the genome. The Genomic analysis, and many others, revealed a cluster of genes closely linked to extreme symptoms on chromosome.[3]

Conclusion

Table 1: *Laboratory Investigation of Cytokine Storm in COVID-19*

Systemic Inflammation	Immunity	Tissue damage	Increased Pre- renal and renal damage
Increase Serum ferritin Increased Serum Pro Calcitonin	Innate Immunity	Increase Serum ALT/AST (Liver damage)	Cl^-, K^+, Na^+ Electrolyte imbalance
Increase Serum CRP	Increase Neutrophils count	Increase Serum D-Dimers (endothelial damage)	Serum Creatinine
Increase Triglycerides	Increase monocytes count	Increase Serum Troponin I (Heart damage)	Serum Creatinine:BUN
Decrease Serum albumin	Adaptive Immunity	Increase Serum LDH (cell death)	GFR
High Serum IL-6	Decrease Lymphocytes/NC	Blood Urea (Kidney)	Urine Protein

Table 2: *Laboratory Investigation of Cytokine Storm Causes when things go Wrong with COVID-19*

Systemic Inflammation and clinical Picture	Tissue damage	Increased Pre- renal and renal damage
Increase serum ferritin Is a mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm	**Increase serum ALT/AST (Liver damage)** Useful for assessment of liver dysfunction associated with hepatic necrosis and hepatocyte destruction.	**Serum Cl^-, K^+, Na^+** Electrolyte imbalance
Increase serum CRP It is useful for detecting systemic inflammatory processes. Increase associated with severity of viremia and sepsis, associated with prognosis	**Increase D-Dimers (endothelial damage).** Raised serum D-dimer (above 1 μg/mL) is a strong and independent risk factor for death in this population.	**High Serum Creatinine** Renal injury, declining renal function, therapeutic dose adjustment
Increased Serum Procalcitonin It is useful for diagnosing Diagnosis of bacteremia and septicemia. It shows bacterial coinfection in those developing severe form of disease.	**Increase Serum Troponin I** (Heart damage) It is useful for assessment of myocardial infarction.	**Serum Creatinine: BUN** It is useful for diagnosing and monitoring treatment of acute and chronic renal diseases - Estimation of Glomerular filtration rate -Adjusting dosage of renal excreted medications
Decrease Serum albumin, It is useful for the assessment of nutritional status and liver dysfunction when low shows impairment and when high shows dehydration	**Increase serum LDH (cell death)** It is useful for the assessment of tissue damage. Its high level shows Indicate severe shock, and hypoxia. Widespread tissue damage particularly pulmonary injury	**Plasma Lactate** It is useful for monitoring of lactic acidosis and its raised level shows septic shock, associated with prognosis

This analysis highlights the unique features of patients with COVID-19 disease that there is an imbalance in cytokine storm players with genomic and laboratory parameters (proinflammatory status, systemic cell death, multi-organ tissue damage, and pre-renal electrolyte imbalance and are predictive of this hyperimmune condition.)

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