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Coronavirus (Covid-19) and Genetics Influence

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ABSTRACT

Background: The pandemic triggered by the Coronavirus 2 Severe Acute Respiratory Syndrome (SARS-CoV-2) has contributed in just a few months to several thousand deaths worldwide. Comorbidities such as asthma, diabetes, and chronic obstructive pulmonary disease also existed in patients who suffered from Coronavirus disease 2019 (COVID-19). The angiotensin- converting enzyme 2 (ACE2) was recognized as a central factor that enables COVID-19 to bind and reach host cells. No research to date has tested the expression of ACE2 in the lungs of patients with these diseases. The gene ACE2 actually encrypts the enzyme-2 which converts angiotensin. Latest research and analysis indicate that ACE2 seems to be the host receptor for the 2019-nCoV / SARS-CoV-2 novel coronavirus. Recent studies have shown the strong association between ACE2 expression and SARS-CoV infection in vitro. A variety of factors of ACE2 may minimize the linkage between ACE2 and S-protein in SARS-CoV or NL63 [66]. Consequently, the degree of expression and pattern of human ACE2 expression in various tissues can be crucial to the sensitivity, effects, and outcome of COVID-19 infection. A recent one- cell RNA-sequencing (RNA-seq) study revealed that Asian males could have a higher ACE2 transcription. As of now the novel coronavirus clinical studies from non-Asian communities are very small for comparison. However, the genetic basis for the expression and role of ACE2 is still mostly unclear in various populations. Hence, genomic study of quantitative feature loci expression (eQTLs) (The GTEx Consortium, 2015) along with more epidemiological studies into the COVID-19 spreading in East Asia (EAS) and other populations need potential functional coding variations in ACE2 across populations. The risk of infection with SARS-CoV-2 in a population is predicted to be affected by clinical behaviors, vaccine availability or prophylactics and the presence of susceptibility genes in the community. Previous research showed that SARS-CoV- 2 cellular absorption requires angiotensin conversion enzyme 2 (ACE-2) and a cellular protease. The spike (S) protein for corona virus binds ACE-2 and acts as an entry receptor. Trans-membrane protease serine 2 (encoded by TMPRSS2) primes the S protein after binding with the receptor to facilitate cellular uptake. Human expression of TMPRSS2 may also be a key determinant of the susceptibility to SARS-CoV-2 infections. Given that the mystery of how COVID-19 destroys, there is an immediate need for a thorough understanding of COVID-19 biology that hampers the capacity of physicians to select medications. All in all, it's fair to assume host genetic factors may play a role in coronavirus (SARS-CoV)-related susceptibility and resistance to SARS. Our key goal in this study is to present the effects of several studies we've performed here in Brazil, with 80 patients with coronavirus under different conditions. We gathered, and sequenced their genetic samples. And the findings show that that 40 percent of Covid-19 affected patients have a higher genetic expression of the genes ACE2 and TMPRSS2. Patients in serious treatment also display a greater expression of inflammatory genes: TNF-A, IL-6, IL-10, IL-18, etc.

Keywords: Coronavirus, Covid-19, SARS-COV2, Coronavirus and Genetics, DNA, Genetics, ACE2.

CORONAVIRUS (COVID-19) AND GENETICS INFLUENCE

ACE2 RECEPTORS AND TMPRSS2

Numerous type of corona-virus spread around the world, infecting humans continuously, usually causing only minor respiratory diseases. Nevertheless, we are now seeing the introduction of a new COVID-19 worldwide. Studies suggest that the new virus, called SARS coronavirus-2, has been transmitted to humans from animals. This triggers a pulmonary illness that may take a dangerous course, called COVID-19. Since December 2019, the SARS-2 COVID has spread, and is closely linked to the SARS coronavirus that caused the 2002/2003 SARS pandemic. Currently vacines are being tested but no drugs are capable of fighting such viruses yet. Quite few experiments have shown that for certain coronaviruses, including COVID-19, the ACE2 receptors are the entry point in human cells. ACE2 (angiotensin I 2 converting enzyme) is a gene which codes for proteins. ACE2-related illnesses include extreme acute respiratory syndrome and Coronavirus outbreak.

ACE2 is a membrane protein required to bind and join the coronavirus into cells.[44,53,67] Upon binding, viral entry is enabled by activating the viral spike glycopro- tein and cleavage of ACE2's C-terminal component by proteases such as TMPRSS2 and FURIN that are conveniently found in lung tissue.[39,70,29] ACE2 is expressed only moderately in normal lung tissue relative to the breast, kidneys and reproductive organs,[14] Nevertheless, staining of the lung tissue portions of adults with pulmonary hypertension revealed elevated ACE2 protein in the pulmonary artery endothelium relative to stable controls.[8] There was also upregulation of ACE2 in

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animal models of liver fibrosis.[35] The explanation for this upregulation remains uncertain, however, and no connection to other COVID-19 comorbidities has been identified.

It may lead some to conclude that declining rates of ACE2 in cells can help combat infection. ACE2 has, however, been shown to have a defensive effect against virus-induced lung damage, through the production of the angiotensin vasodilator 1-7. Yes, the association of the virus protein with ACE2 causes a reduction in ACE2 levels in cells, possibly leading to lung damage. In certain terms, the association between ACE2 and the frequency of infections with coronavirus is paradoxical, and hard to anticipate. Additionally, it has been seen that accessible blockers (AT1R) or angiotensin II receptor blockers such as Losartan raise the volume of ACE2, plausibly promoting infection. As such, suggestions that the available AT1R blockers can help to cure COVID- 19 need to be checked by clinical reports of patients. Suggestions that high doses of vitamin D, which have been shown to improve ACE2 production in cells, could be successful in the battle against infection, have a related implication. One way to counter infection may be by administering soluble ACE2 into the bloodstream, which would have the secondary effect of interfering with cellular ACE2, thereby stopping the virus from binding to uninfected cells and replenishing ACE2 into infected cells.

Alternative studies have indicated a strong correlation between hypertension and heart disease and COVID- 19, which could be attributed to the fact that these patients usually undergo ACE inhibitors, thus enhancing the supply of ACE2 sites for the virus to infect cells.

The coronavirus' "max" of the new SARS-CoV-2 binding protein uses the same cell binding factor (ACE2) as SARS-CoV, which uses the TMPRSS2 cell protease for activation. Existing clinically approved medications which target TMPRSS2 can inhibit lung cell infection with SARS-CoV-2.

Transmembrane serine protease type II (TMPRSS2) stimulates COVID-19 for entry into cells that in infected humans are normally vulnerable to infection. An important feature of the TMPRSS2 gene is the location of several androgen receptor elements (AREs) upstream of the transcription starting site and the first intron.[9,32] The TMPRSS2 gene encodes a predicted 492 amino acid protein that anches the plasma membrane. It transforms between Arg255 and Ile256 to form by autocatalytic cleavage. The mature proteases are largely membrane-bound after cleavage, but a small portion of them can be released into the extracellular environment. The catalytic protease domain contains a catalytic triad consisting of the His296, Asp345 and Ser441 amino acid residues, corresponding to chymotrypsinogen His57, Asp102 and Ser195.[9,32] TMPRSS2 is found primarily in breast, with comparatively lower rates of expression in the lungs, colon, liver, kidneys, and pancreas. TMPRSS2 is expressed in an androgen-dependent manner in lung cancer cell line A549 and the prostate cancer cell line LnCaP.[38] It has been shown that TMPRSS2 stimulates protease-activated receptor 2, a G-protein coupled receptor, and that PAR-2 activation induces upregulation of the metalloproteinase-2 (MMP-2) and MMP-9 complex, both of which are main proteases in the tumor cell metastasis.[65] In addition, the hepatocyte growth factor (HGF) activated by TMPRSS2 facilitates c-Met receptor tyrosine kinase signaling and induces a pro-invasive epithelial-mesenchymal transformation phenotype in prostate cancer cells. A recent research suggested that TMPRSS2 plays a role in cancer pain and pain generally as a cell membrane-anchored mediator.[20] TMPRSS2-deficient mice, however, did not display any apparent phenotypic abnormality such as death, miscar- riage or visible illness, and the precise physiological role of TMPRSS2 in vivo remains unclear. It is hypothe- sized that TMPRSS2 may contribute to a specialized but non-vital role which only becomes evident under certain conditions.[62]

COVID-19 uses the SARS55 CoV receptor, ACE2, for information, and the TMPRSS2 serine protease for activation of protein S. A legally accepted TMPRSS2 inhibitor has blocked entry, and could be an alternative for treatment. Our results show important differences between SARS-CoV-2 and SARS-CoV and identify a possible target for antiviral action.

Camostato's drug mesostat inhibits the TMPRSS2 protease; the researchers also investigated whether the drug can also prevent SARS-CoV-2 infection. Their findings also indicate that mesylate camostat can also offer defense against COVID-19. Genetic factors can play a role in the susceptibility and resistance to SARS, an infection infected with coronavirus (SARS-CoV).

INFLAMMATORY RISK (CYTOKINE STORM)

The cytokine storm refers to the overproduction of inflammatory cytokines from a wide range of biological activity from a number of tissues and cells (mainly immune cells), triggered by multiple infections and a lack of negative feedback on the immune system. Such cytokines, in effect, drive positive feedback on other immune cells and proceed to recruit them at inflammatory sites, engendering accelerated inflammatory growth and organ destruction. In short, it is the autoimmune system's incessant intense activation and attack.[25]

The cytokine earthquake, and the consequent ARDS, stems from the actions of several immune-active molecules interacting together. Interferons, interleukins, chemokines, colony-stimulating

factors and TNF-alpha are the key components of the cytokine storm's produc- tion and will be briefly examined.

Interferons: A cytokine family with a central role in virus-driven innate immunity binds specific receptors and results in the expression of anti-viral or immunomod- ulatory protein encoding genes. This series of events promoted the clinical application of IFNs in many infectious diseases such as chronic hepatitis but also in non-viral illnesses such as leukemia , lymphoma, melanoma and multiple sclerosis.[27,58]

Tumor necrosis factor α (TNFα): It a pyrogen cytokine released from the immune cells during the acute inflam- mation and infection processes. This is a key cytokine in infectious infections and is associated with many chronic autoimmune and inflammatory disorders.[68]

Colony-stimulating factors (CSF): These proteins are associated with inflammatory conditions and are components of an amplification cascade that eventually enhances the production of cytokine by macrophages at inflammatory sites. This influence holds the inflammatory response running.[28]

Interleukins: A family of cytokines participate in the division and control of immune cells. They mediate immune cell traffic to the site of the infection, induce increased signaling of the acute phase, activate epithe- lial cells and mediate secondary cytokine production. Interleukin-6 (IL-6) among them deserves a more compre- hensive review given its role in the cytokine storm triggered by coronavirus. Due to its role in controlling acute phase response, IL-6 is crucially involved in acute inflammation[59]. Nearly all stromal cells and B lympho- cytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells, and other non-lymphocytic cells, such as fibroblasts, endothelial cells, keratinocytes, glomerular Mesangial cells, and tumor cells, generate it. IL-1β and tumor necrosis factor (TNF-α) enhance the production of this cytokine. IL-6 can also be responsible for initiating the dendritic cell-T cell association of T helper 17 (TH17) cells. For patients affected by COVID-19, high activa- tion of TH17 cells may result from an increased develop- ment of IL-6 by the immune system induced by viruses. Thanks to its pleiotropic properties IL-6 plays a crucial role in the pathogenesis of the cytokine outbreak. Several studies have found that plasma levels of IL-6 in COVID- 19 patients are elevated and that their circulating levels are strongly related to seriousness of the disease. High serum IL-6 levels have been proposed as predictors for serious- ness of the disease for this cause. Indeed, in animal models of SARS-CoV infection, inhibition of the transcription factor of IL-6 was associated with reduced mortality, and in effect of its development.[57]

Use of Tocilizumab as a preventive agent was introduced during the latest COVID-19 pandemic. Tocilizumab is an IgG1 monoclonal, humanized anti-IL-6 receptor antibody used to treat rheumatoid arthritis and other systemic inflammatory diseases. By blocking the interaction of the IL-6 receptor, tocilizumab prevents the transduction of the IL-6-mediated signal. Although clinical results on the use of tocilizumab in COVID-19 patients was drawn from limited sequence, some writers suggest its use in critically ill COVID-19 patients with substantially elevated levels of IL-6.[22]

Chemokines: We are a broad family of cytokines with a strong chemical influence. Chemokines serve as chemo- attractants in the movement of cells in the immune system, but they are also active in many other mechanisms including the development and action of the innate and adaptive immune system, embryogenesis and cancer metastasis. They are secreted promptly by a number of cells in response to viral or microbial infections.[36]

Chemokines function as powerful chemo attractants and, according to a chemokine gradient, recruit inflamma- tory cells to migrate from the intravascular space via the endothelium and epithelium into the inflammation location. The function of one particular chemokine, CXCL10 (previously referred to as 10 kDa inducible interferon-y protein, or IP-10), has been highlighted in both experimental and patient models in ARDS.

In addition, an up-regulation of the mouse CXCL10 analog mob-1 mRNA was observed in a mouse model of IL-2 -mediated ARDS at the initiation of lung injury (Neville & Abdullah, 1995). Numerous studies have also demonstrated that intratracheal mob-1 injection in mice induced pulmonary leukocyte migration in the alveolar space, with significant neutrophil recruitment, particularly monocytes. This incident was accompanied immediately by microvascular damage and ARDS-typical pulmonary edema. CXCL10 signaling tends to be a key factor in the initiation of ARDS, as seen in ARDS mice caused either by acid aspiration or by viral infection (influenza H5N1 virus). Briefly, Ichikawa et al. showed that wild-type mice forming ARDS had elevated levels of CXCL10 primarily due to increased secretion by invasion of neutrophils, which caused an autocrine loop process on the chemotaxis of inflamed neutrophils, contributing to fulminant pulmonary inflammation. By comparison, CXCL10 and/or its CXCR3 receptor knock-out mice displayed reduced severity of lung injury and improved survival in response to both viral and non-viral lung injury[4]. In addition, CXCL10 expression in the lung was substantially up-regulated following induction of ARDS with Lipopolysaccharide (LPS) in a lung injury model of the mouse, and neutralization of CXCL10 with anti-CXCL10 antibody contributes to lung injury improvement.[21]

CXCL8 (also known as IL-8) is another chemokine regarded as a possible bio-marker for the clinical course of ARDS.[30] Indeed, CXCL8 levels in patients with ARDS have been shown to be elevated in both plasma and broncho-alveolar lavage fluid. In rabbit with acid- induced ARDS, a direct function of CXCL8 in ARDS development has been shown to lead to a 10-fold rise in CXCL8 levels in alveolar fluids. Note that pretreatment with an anti-CXCL8 antibody prevented the occurrence of normal acute injury to the lungs.[72]

Storms of cytokines can cause serious damage to body tissues and organs. For example, if a cytokine storm occurs in the lungs fluids and immune cells, such as macrophages, can accumulate and eventually block the airways, leading to death.

Evidence shows the cytokine outbreak may be related to the seriousness of the disease. Increases serum expression of IL-2R and IL-6 interleukins can predict severity and prognosis of COVID-19 patients.

In extreme cases, immunomodulating agents targeting the large cytokines found in COVID-19 will also serve to relieve the effects of hyperinflation. In patients with COVID-19, elevated levels of the inflammatory predictor IL-6 in the blood were identified as predictive of a fatal outcome.

LITERATURE REVIEW

A research was undertaken to explore the relationship in the Chinese Han population between the genetic polymor- phisms of the OAS1 gene, as well as the MxA resistance and the susceptibility gene SARS. A case-control analysis of the hospital was performed with 66 cases of SARS, which included 64 samples not compromised by direct contact. Results indicated that polymorphism was associ- ated with SARS infection in the 3'- untranslated (3'- UTR) region of the gene OAS1. Relative to the AA genotype, 0.42 (0.20 ~ 0.89) and 0.30 (0.09 ~ 0, 97) were shown to be the AG and GG genotypes correlated with a defensive impact against SARS contamination by ORs (95 percent CI). Furthermore, a GT genotype in the MxA gene promoter at position 88 was associated with an improved susceptibility to SARS infection relative to a GG genotype (OR = 3.06, 95 percent CI: 1.25 ~ 7.50). AG genotype associations in OAS1 and GT in MxA remained signifi- cant in multivariate analyzes after adjustment for SARS protection measures (OR = 0.38, 95 per cent CI: 0.14 ~ 0.98 and OR = 3.22, 95 per cent CI: 1.13 ~ 9.18, respec- tively).[26]

A case-control research was performed in an Iranian population to examine the interaction of polymorphisms in inflammatory cytokine genes with influenza patients and the ILI community. Real-time RT-PCR and HI assays confirmed the overall number of 30 influenza B, 50 influenza A (H1N1) and 96 persons hospitalized with ILI. The determination of genotype in the genes IL-1β, IL-17, IL-10 and IL-28 was evaluated for identified SNPs. The IL-1β rs16944 (P = 0.007) and IL-17 rs2275913
(P = 0.006) genotypes were associated with serious influenza disease while the IL-10 rs1800872 and IL- 28 rs809917 frequencies were not associated with the disease (P > 0.05). In fact, the lack of A allele in IL-17 rs2275913 SNP raised the chance of influenza A infection (H1N1) (P = 0.008). This research found that influenza A- (H1N1) and B-infected patients and even ILI controls had different immune parameter profiles, and persons with unique cytokine-derived polymorphisms can have differing immune responses to extreme outcomes.[61]

The observational study analyzed more than 700 lung transcriptome samples of patients with significant COVID-19-related comorbidities and observed that ACE2 was strongly expressed in these patients relative to individual controls. This result indicates that patients with these comorbidities could be more likely to experience serious COVID-19. We also identified other genes, such as RAB1A, which could be essential to lung infection with SARS-CoV-2. Correlation and network analysis revealed many potential human lung ACE2 regulators, including genes associated with histone modifications, such as HAT1, HDAC2, and KDM5B. Epigenetic marks found in locus ACE2 were in fact consistent with those supported by KDMSB.[19]

Another investigation emerged when multiple large genome databases, including the GTEx portal, SNP nexus, and Ensemble genome project, were used to identify gene expression profiles for TMPRSS2 and its significant expression of quantitative trait loci. Data suggest that four variants (rs464397, rs469390, rs2070788, and rs383510) impair TMPRSS2 expression in the lung tissues. In global populations, including African, American, European and three Asian cohorts (China, Japan, and Taiwan), the allele frequency of each type was then measured. Interestingly, the results show that TMPRSS2-upregulating variants are higher in European and American populations than in Asian populations, which means that these populations may be relatively susceptible to infection with SARS- CoV-2.[1]

A further analysis of the sample was carried out to analyze the virus patterns in terms of various variables. A differential expression of ACE2 and TMPRSS2 was observed in nasal and bronchial airways according to age and condition of illnesses. Kids in upper and lower airways (nasal and bronchial) were shown to have slightly reduced expression of COVID-19 receptors. In comparison, both ACE2 and TMPRSS2 lung airway expression are shown to be dramatically upregulated in smoking relative to non-smokers, and in patients

with chronic obstructive pulmonary disease (COPD) relative to safe subjects. No disparity was found between children and adults in ACE2 and TMPRSS2 blood expression levels, including in COPD including diabetic patients. Nevertheless, in patients with critical hypertension, a substantial rise in blood expression rates of both genes was found, although only ACE2 was upregulated in the asthmatic blood. These findings indicate that the reported disparity in frequency of COVID-19 between children and adults may be due in part to the variation in levels of expression of tissue in the airways ACE2 and TMPRSS2 (Sharif-Askari, et al., 2020).

The meta-analysis of the genes (and proteins) of ACE2, TMPRSS2 and CTSB / L in public library repositories and found that they are all commonly distributed in human tissues; also, the genes of ACE2 and TMPRSS2 appear to co-regulate. The expression of ACE2 and TMPRSS genes is (among others) inhibited by TNF, which is caused by pro-inflammatory disorders like obesity, Barrett's esophagus, helicobacter pylori stomach inflammation, asthma, autoimmune diseases which oxidized LDL; exercise, as well as growth factors, infections of bacteria, tobacco smoking, interferons and androgens. Among the therapies presently being studied, interferon-beta mediated gene expression of ACE2 in bronchial epithelial cells while chloroquine appears to upregulate CTSB / L genes. Finally, we analyzed the ACE2, TMPRSS2 and CTSB / L modulated KEGG pathways and tested DrugBank for drugs that target the affected pathways modules.[52]

There is a short report on the vitamin D and SARS-CoV- 2 virus / COVID-19 disease which provides a balanced scientific view. This includes a concise overview of recent medical research associating vitamin D, pneumo- nia, upper respiratory tract infections (URTIs) and immune function. The paper ends with dietary approaches to prevent shortages in vitamin D and maintain a safe, nutritious diet at all time, even during the latest pandemic.[45]

METHOD

For this study we carried out experiments with positively tested COVID-19 on the group of people from the same area but with different genders and age. We performed a case-control analysis on specimens collected from patients in Brazil. Those specimens collected from the patients with their written permission, which was received from all participants and accepted by FullDNA Bioethics Commission. Studies were carried out among citizens in Brazil who preferred not being identified due to data protection regulations. The overall number of people who took part in the survey was 319, of which 178 were males and 141 females. Such patients were aged between 18 and 62 years, with COVID-19 taking various stages. And the method / medium of their virus interaction is unclear. Remember that not diabetics, not smoking, not cancer patients and not oncology patients are all members of the study community. We gathered and sequenced their genetic samples.

Cases and controls

The analysis included a total of 319 confirmed cases of SARS. They were identified according to guidelines provided by the Ministry of Public Health of Brazil, and then confirmed by serological examination. There were good doctors and nurses operating at hospitals, with a tradition of near interaction with people suffering from SARS. When a person had shared a meal, utensil, home, hospital, car, etc. with a SARS patient or had seen a patient, the person's contact history was made. Furthermore, contagion was often used as close touch. All the tests against COVID-19 is negative for an IgG antibody. Some reviews which are consanguineous of any situation have been omitted.

Information collected using a questionnaire

A questionnaire was created to obtain information from all cases and controls on demographic identifiers (age, gender, place of origin, etc.), behaviors and medical background (smoking and drinking habits, diet, exercise, dental background, history of operations, etc.), and safety precautions (wearing helmets, gowns and goggles while in touch with SARS patients). All the cases and tests carried out in the questionnaire before supplying DNA samples. All delegates signed a written consent. This study protocol was according to the National Center for AIDS Prevention and Control policies.

DNA extraction

The genomic DNA was collected using a cell DNA extraction kit (FullDNA Swab) as directed by the manufacturer.

RESULTS AND DISCUSSION

The results show Normal, Average and High levels. Average Levels correspond to heterozygous (+/-) and High Levels correspond to Homozygous (+/+).

The results showed that out of 178 tested males, 28 had higher predisposition to a higher expression of ACE2 and 26 to TMPRSS2. Whereas, out of 141 tested females 23 had higher predisposition to a higher expression of ACE2 and 22 to TMPRSS2.

Out of 178 tested male, 21 have higher expression of IL-6. On the other hand, out of 141 tested female, 16 had higher expression of IL-6.

Out of 178 tested males, 150 (126 + 24, Average + High Levels of Deficiency) have a lower Vitamin C serum level genetic susceptibility. While out of 141 tested females, 118 (101+17, Average + High Levels of Deficiency) have a lower Vitamin C serum level genetic susceptibility.

Out of 178 tested males, 174 (167+7, Average + High Levels of Deficiency) have a lower Vitamin D

serum level genetic susceptibility. However, out of 141 tested females 138 (132+6, Average + High Levels of Deficiency) have a lower Vitamin D serum level genetic susceptibility.

Now we will discuss each of the results separately in the light of research based evidence.

ACE2 Expression in Different Genders:

Some of the sex hormones affect the homeostasis of RAS. Although the ACE2 activity showed no difference between the male and female,[71] the males have higher expression levels of ACE2 in the lungs compared to the females. Moreover, at least five types of cells in the lungs from the males express ACE2, while only two to four types in the female's lungs do so.[49] Consistent with these findings, the SARS-CoV-2 infected males were slightly but not statistically significantly higher than the females (58.1 % vs. 41.9 %) in a survey included 1099 patients.[64] The female sex hormones may affect ACE2. The ACE/ACE2 activity ratio in the male serum is higher than that in the females, which may partially attribute to the activation effect of estrogen on ACE2 activity.[37] During pregnancy, the fluctuation of hormones may drastically change the expression of ACE2 both in the reproductive system and in other organs. The ACE2 mRNA expression in the uterus of pregnant rats was significantly higher than the one in the unpregnant rats [15], indicating the implication of progesterone in the regulation of ACE2 expression.[17] Similar up-regulation of ACE2 expres- sion was also found in the kidneys of pregnant rats.[47]

These results suggested that pregnant women infected with SARS-CoV-2 should be watched for severe compli- cations and rapid progression.

ACE2 Expression during Aging:

According to the data which collected 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in mainland China, the average age of the severe patients (n = 173) was significantly older than the non- severe ones (n = 926) by seven years.[64] Among the critically ill COVID-19 patients, the non-survivors (64.6 years) were older than the survivors (51.9 years).[63] These data indicated that aging might be correlated with the pathological progression and poor prognosis of COVID-19. Results obtained from the genetic knockout mice model demonstrated that ACE2 depletion caused physiological early aging independent of Ang (1-7), indicating the regulatory role of ACE2 in aging.[41] ACE2 expression in the lungs may decrease during aging according to the results in aged rats.[54] In humans, the ACE2 activity did not differ from the young and aged males but showed significant difference in the young and aged females. This finding indicated that the effect of aging in ACE2 activity might have a gender difference. In a study that included 220 healthy Chinese volunteers, young Chinese females showed significantly higher ACE2 activity than aged females. However, the activity of ACE2 in women during aging is controversial, as a Spanish group reported lower ACE2 activity in the young females comparing to the aged females.[37,71] Such controversy may due to sample number-induced deviation or race, which requires further validation and investigation.

Table 1: The results show Normal, Average and High levels. Average Levels correspond to heterozygous (+/-) and High Levels correspond to Homozygous (+/+).

	Normal Levels		Average Levels		High Levels		n
	Male	Female	Male	Female	Male	Female	
ACE2	67	54	82	65	28	23	319
TMPRSS2	72	48	83	68	26	22	319
IL-1B	4	3	134	105	41	32	319
IL-6	35	28	123	96	21	16	319
IL-10	9	7	114	91	56	42	319
CCL-2 (MCP-1)	97	77	57	45	24	19	319
IFN-G (Interferon Gamma)	28	22	133	105	17	14	319
Vitamin C Serum (Deficiency)	28	23	126	101	24	17	319
Vitamin D Serum (Deficiency)	4	3	167	132	7	6	319

ACE2 Expression during Development:

Although children of all ages were susceptible to COVID- 19, accumulating clinical data indicated lower infection rates and better clinical outcomes in children compared with adults.[56] Recently, a retrospective study analyzed clinical data from 2135 pediatric cases with COVID-19 and found that over 90 % of these pediatric patients were asymptomatic, mild, or moderate cases. Although there currently lacks an explanation to this phenomenon, the authors speculated a potential implication of ACE2.[7]

Results in the animal studies implied that ACE2 expres- sion in adults might be higher than that in children. Sheep could be used as an animal model for studying the development of RAS. The expression of ACE2 was signif- icantly lower in the neonatal sheep comparing to that in the adult ones.[23] This finding seems to indicate that lower

ACE2 expression might be correlated with the lower susceptibility of children to SARS-CoV-2. However, the expression and activity of ACE2 during the development of human children and teenagers are largely unclear.[7] SARS-CoV and TMPRSS2 Protease:

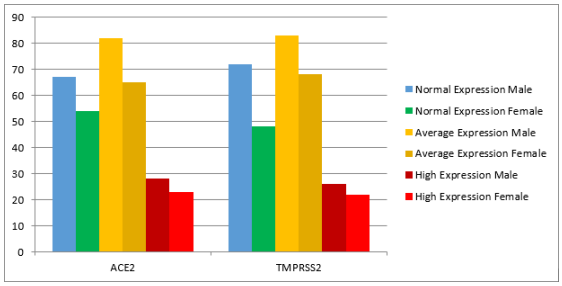

Figure 1: ACE2 and TMPRSS2 expressions on different patients

The SARS-CoV S protein can be cleaved by a wide variety of host proteases, such as TMPRSS2, HAT, MSPL, DESC1, Factor Xa and cathepsin L/B.[48] It has been shown that SARS-CoV enters into cells via two distinct pathways: one is mediated by TMPRSS2 at the cell surface and the other done by cathep- sin L/B in the endosome.[12] The serine protease inhibitor camostat can effectively protect mice infected with the otherwise lethal SARS-CoV from death, but treatment with both serine and cathepsin inhibitors failed to improve survival significantly over that achieved with camostat alone,[16] indicating that SARS-CoV propagation and pathogenesis is mediated by TMPRSS2 rather than cathepsin in vivo. Kawase et al. found that SARS-CoV entry increased 2.6-fold in the presence of TMPRSS2; conversely, siRNA targeting TMPRSS2 caused a five-fold decrease in SARS-CoV entry into Calu-3 cells.[10] Moreover, the levels of SARS-CoV RNA are nine-fold higher in cells expressing active TMPRSS2 than in cells expressing enzymatically inactive TMPRSS2 (S441A) [70]. Western blot analysis revealed that SARS-CoV S is cleaved into several fragments upon expression of TMPRSS2 (cis-cleavage) in the infected cells as well as upon contact between SARS- CoV S-expressing cells and TMPRSS2-expressing cells (trans-cleavage). Cis-cleavage results in the release of SARS-CoV S fragments into the cellular supernatant, which may interfere with antibody-mediated neutraliza- tion. Trans-cleavage activates SARS-CoV S on the target cell, allowing for efficient SARS-CoV S-driven viral fusion.[13] In addition, the activation of SARS-CoV by TMPRSS2 interferes with the inhibition of SARS-CoA S by Interferon-induced transmembrane proteins (IFITMs), a class of interferon-induced host cell proteins that inhibit the entry of several enveloped viruses. Collectively, the obtained evidence suggests that TMPRSS2 plays an important role in SARS-CoV infection.[33] The host proteases involved in the priming of MERS-CoV include TMPRSS2, HAT, MSPL, DESC1, furin and endoso- mal cathepsin B/L. Similar to SARS-CoV infection, MERS-CoV infection is largely dependent on the activity of endogenous TTSPs. Camostat treatment alone is as effective as camostat plus EST, a cathepsin inhibitor, in the inhibition of virus entry into Calu-3 cells, indicat- ing a dominant role of TMPRSS2 in MERS-CoV entry. Indeed, TMPRSS2 augments MERS-CoV infection by up to 100-fold in Vero cells. A non-catalytic TMPRSS2 (S441A) significantly abrogated the entry of MERS- CoV compared to normal TMPRSS2.[2] Although other host proteases such as HAT, MSPL and DESC1 have been suggested to be involved in the priming of MERS- CoV, their expression levels in lung tissue are consider- ably lower than that of TMPRSS2, indicating a limited role of these proteases in viral propagation in host lung tissue. These observations demonstrate that MERS-CoV infection is largely dependent on the activity of endoge- nous TMPRSS2.

Enzymes Involved In the Cytokines Storm in COVID-19: Emerging data suggest that many patients infected with COVID-19 may die due to an excessive response from their immune system, characterized by the abnormal release of circulating cytokines, called cytokine release syndrome. This syndrome plays an important role in the deterioration of patients with COVID-19, from pneumonia to acute respiratory syndrome, accumulating systemic inflammation and, finally, organ failure. This phenomenon characterized by a multitude of cytokines wreaking havoc throughout the body is often called a ”cytokine storm”.

Many cytokines participate in the “cytokine storm” in patients with COVID-19, including IL-6, IL-1, IL-2, IL- 10, TNF-α and IFN-γ; however, a crucial role is played by IL-6, whose increased serum levels have been correlated with respiratory failure, acute respiratory syndrome and adverse clinical outcomes. IL-6 has significant pro-inflammatory properties and works through two main signaling pathways: cis or trans. SARS-CoV and Deficiency in Vitamin C & D:

The continued spread of the novel SARS-CoV-2 virus, and the disease COVID-19 that is caused by SARS-CoV- 2, has led to calls for widespread high-dose vitamin D supplementation.[24,50] These calls are without support from pertinent studies in humans at this time, but rather based on speculations about presumed mechanisms. There have been two key studies published to support this presumption:

An unbiased screen of repurposed drugs for treatment of avian influenza A H5N1 virus using appropriate cell lines and mice, which highlighted calcitriol (the active hormone of vitamin D) as a potential therapy.[22]

A recent analysis of vitamin D and viral infections.

However, whether these mechanisms apply with SARS- CoV-2 is not known. Studies investigating vitamin D and COVID-19 are currently underway (Chinese Clinical Trials Registry, 2020) and more are likely to follow. Given that ethnic minorities are disproportionately affected with Covid-19—and this appears to be the case principally in the UK, the USA and other European countries— further research is justified, especially given that there is clear evidence that vitamin D deficiency is particularly common in these ethnic group.[51]

However, we strongly caution against doses higher than the upper limit (4000 IU/day; 100 µg/day); and certainly of very high doses of vitamin D (in some reports, 10 000 IU/day (250 µg/day) of vitamin D are being promoted) unless under personal medical advice/clinical advice by a qualified health professional. Instead, we advocate the following lifestyle strategies for avoiding vitamin D deficiency and ensuring a healthy, balanced diet (Institute of Medicine, 2011).

Interestingly, recent studies in Italy have suggested that the greater COVID-19 mortality cases in Northern Italy may likely be related to the higher levels of pollution compared with other Southern Italian regions. It may very well be that many Northern Italians are at a suboptimal state of vitamin C status, or even at a state of deficiency – due to pollution-induced depletions – potentially compromising nutrient associated immune functions (V, 2020).

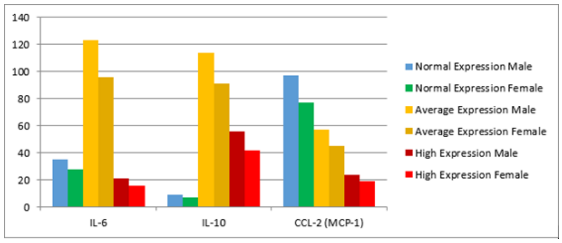

Figure 2: Cytokines expressions in Males and Females

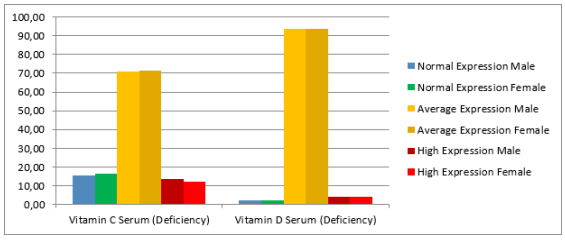

Figure 3: Vitamin C and Vitamin D related deficiencies

Perhaps, the reduction of the cytokines storm in the late stages of the Covid19 infection is the most significant application of IV Vit-C. Covid19 pneumonia is a complex medical disorder with high morbidity and mortality rate. This causes severe lung injury that results in Acute Respiratory Distress Syndrome (ARDS), a life- threatening lung disorder. This process prevents the necessary oxygen to enter into the lungs and ultimately causes death. Coronaviruses increase oxidative stress that promotes cellular malfunction and ultimately results in organ failure. It is believed that pulmonary failure (ARDS) is the principal cause of Covid19′s action on humans. This helps to increase oxidative stress considerably because of the generation of free radicals and cytokines. This process finally leads to serious cellular injury, organ failure and death. The administration of anti-oxidizing agents along with proven conventional supportive therapies is believed to have an important role in controlling these medical situations. Appropriate vaccines and antiviral drugs for the Covid19 epidemic are not available. IV Vitamin C and other antioxidants are extremely good agents for ARDS. These can be applied clinically. Importantly, high dose IV Vit-C is safe and effective. In this paper, we review the use of high-dose Vit-C as an efficient method of treatment for patients with cancers and infections.[34]

CONCLUSION

The emergence of infectious disease is one of the most important impacts of the increasing rise in human migration and globalization. The influenza and coronavirus epidemics have existed around the world since the beginning of the 21st century. The rise of drug- resistant viruses and novel strains underlines the need for modern antiviral methods and approaches. Targeting cellular factors is a fairly recent antiviral technique which can limit or discourage the proliferation of mutants from escaping. In addition, we found that people with higher expression of genetic markers ACE2 and TMPRSS2 were about 40 per cent more prone to Covid-19. Even individ- uals with a higher expression of genetic markers IL-6, IL-10, IL-18, TNF-A are more vulnerable to a extreme stage due to a greater predisposition to cytokine wind. Those with lower vitamin C and vitamin D serums may have a greater predisposition to Covid-19.

ACE2 is currently under intense study because it is the SARS-CoV-2 receptor, the novel coronavirus that causes the pandemic COVID-19. They summarized the rapidly new COVID-19 results and addressed the possible role of ACE2 in COVID-19 pathogenesis, development and prognosis. SARS-CoV-2 vulnerability in different populations tended to correlate with degree ACE2. The distribution of target organs vulnerable to the SARS- CoV-2 infection and COVID-19 complications is close to that of ACE2. The three functions of ACE2, a peptidase that negatively modulates RAS, an amino acid transport regulator in the kidneys, and a virus receptor, namely SARS-CoV-2 and SARS-CoV, along with the local tissue damage defensive effect, are involved in COVID-19's development and prognosis. These findings indicated that the use of hrsACE2 or ACE2 activator to target ACE2 could

be a potential therapeutic strategy for COVID-19. In COVID-19 patients, prescribing of medications which can affect ACE2, such as ACEI and ARB, requires careful monitoring of blood pressure and COVID-19 progression. TMPRSS2 is also one of the host factors necessary for the pneumotropy and pathogenicity of Asian H7N9 influenza A virus and many H1N1 subtype influenza A virus infections; this enzyme also plays an significant role in SARS-CoV and MERS-CoV infections, suggesting that it is a potential drug target for the treatment of these viral infections. While there are not yet available FDA- licensed inhibitors that directly inhibit TMPRSS2, certain medications such as Camostat and Nafamostat that have inhibitory action against a number of serine proteases have been approved to treat certain diseases as well as to prevent influenza virus and coronavirus infections. Since these drugs suppress TMPRSS2 in vitro and in vivo, repositioning drugs may aid in designing new methods to prevent successful viral entry and replication. Taken together, the data available indicates that TMPRSS2 is likely to be a priority for new therapies for influenza virus and coronavirus infections.

The inflammatory response is an integral part of the immune system to its function; otherwise, it will be hard to remove pathogens. SARS-CoV-2 may induce excessive and prolonged cytokine responses, causing damage to the lungs and multiple organ failures. To date, most studies have focused on the direct measurement of those cytokines and chemokines in the peripheral blood, but in the context of the rapidly changing cytokine environment following infection with the virus, we do not fully understand the cause of the vigorous inflammatory response.

While current trials have demonstrated that a violent cytokine storm causing immune pathological harm may be a real ”monster” in critically ill patients during the outbreak of pathogenic hCOV infection. Around the same time, experiments on human autopsy and animal models have provided some support for the pathogenic role of IMM-derived inflammatory cytokines and neutrophils. Current findings, however, are minimal, and comprehen- sive concepts of molecular biology and wider epidemi- ology are missing. Future research will also concentrate not only on discovering different inflammatory response signalling mechanisms in hCoV-infected patients and animals, but also on the practical and successful method to monitor the dissemination of the virus worldwide.

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