REVIEW ARTICLE

Expression Profile and Implications of ACE2; The Receptor for New SARS-CoV-2

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ABSTRACT

Expansion of novel coronavirus disease 2019 (COVID-19) involves various risk factors including clinical, genetic, demographic and environmental manifestation but they are insufficient to explain disease pathogenesis. With patients ranging from completely asymptomatic to many suffering mild to severe illness, indicates that COVID-19 should better be studied at genetic level as different genetic backgrounds predispose to variability in infection susceptibility. Recently, it is recognized that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds and internalized by the host cells through cell surface receptors angiotensin-converting enzyme 2 (ACE2), which is expressed significantly in variety of human tissues particularly in the lower and upper respiratory tract. To scrutinize the expression profiles and clinical implications of ACE2 gene in humans, literature was extensively reviewed. In common, various studies reported that ACE2 receptor protein is highly conserved among different species, the expression pattern is tissue specific mainly observed in cardiovascular system, breast cells, testis, adipose tissue, kidney, lymphocytes and gastrointestinal system other than the upper and lower respiratory tract. This significant expression makes these organs vulnerable to SARS-CoV-2 virus and hence many comorbidities may be observed during the course of infection. The present review on expression profile of ACE2 not only proposes potential clues for COVID-19 pathogenesis but also designate clinical values of ACE2 gene in heterogeneous disorders.

Key Words: *Angiotensin, ACE2, COVID-19, SARS-CoV-2.*

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A novel and more infectious virus appeared in China at the end of the year 2019, nearly 20 years of epidemic of the severe acute respiratory syndrome (SARS), caused by a beta coronavirus, recently retitled as SARS-CoV-1. This new virus extended across the globe, and finally attained the apex of pandemic disease.[1] As of mid-August 2020, this new coronavirus infected over 20 million people, resulting in at least 739,526 deaths.

Coronavirus disease 2019 (COVID-19) is a heterogeneous group of disorders varied from asymptomatic to very aggressive illness. Demographic, environmental and clinical factors have contributed towards the severity and progression of the disease. The broad inter-individual variation of the disease susceptibility can be explained through predisposing genetic background of the individuals. It has been remarkably established that the virus SARS-CoV-2 is responsible for causing COVID-19, it binds and internalized by the host cell through cell surface protein "angiotensin-converting enzyme 2 (ACE2)".[2] ACE2 is a cell surface receptor, which exhibits its expression in variety of human tissues especially in the respiratory tract, heart, testis, adipose tissue, kidney, lymphocytes and gastrointestinal system.

Angiotensin-converting enzyme 2 (ACE2) gene

ACE2 gene is mapped on chromosome: Xp22.2, it comprises 18 exons and covers approximately 40 kb region in the genome, it encodes for the protein which is 805 amino-acids long and is member of the family of angiotensin-converting enzyme related carboxydipeptidases. ACE2 contains an N-terminal (17-amino-acid) signal peptide and a C-terminal membrane anchor (22 amino acids) and have 40% sequence homology to the human ACE-1 protein.[3] Based on its chromosomal location (Xp22.2), ACE2 gene is hemizygous in males and can be

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heterozygous only in females.[4] Transmembrane serine protease-2 (TMPRSS2) is required for the priming of SARS-COV-2 spike protein and its proteolytic activity is involved in pathogenicity and viral transmission.[5,6] The androgen receptor (AR) is the only known regulator for transcription and modulation of TMPRSS2 gene, which co-expressed with ACE2 gene[7], suggesting that higher concentrations of testosterone in males compared to females may lead to male predominance of severe COVID-19 infection.[8] The levels of soluble ACE2 (sACE2) are same in both sexes till 12 years of age. However, with growing age, its concentrations increase more in boys compared to girls. At the age of 15 years and above, sACE2 is markedly higher in males than females and may contribute to increases risk of severe COVID-19.[9]

ACE2 as a major component of RAS pathway

Angiotensin-converting enzyme or ACE2 plays a crucial role in humans as it is major element of renin-angiotensin system (RAS), which regulates the blood pressure by maintaining the body fluid contents. The main function of ACE2 in this pathway is to convert the angiotensin II hormone into angiotensin 1–7 (Ang 1-7)[10], thus regulating the balance of circulating AngII/Ang1-7 levels.[11] As angiotensin I-7 induces the vasodilation and angiotensin II induces vasoconstriction, therefore ACE2 is responsible to control blood pressure and prevent organ damage by converting angiotensin II into a vasodilator. Angiotensin II is also known to cause pro-oxidative, pro inflammatory and pro-fibrotic activities that cause organ damage.

ACE2 expression profile and related pathophysiology

ACE2 remains in debates since past for its expression in various human tissues (Figure 1). Recently it is recognized as the main receptor for the penetrance of SARS-CoV-2 into target cells. Subsequently, various studies started evaluating the expression profile of ACE2 and the type of the cells in which ACE2 is expressed.[12] Harmer et al. found that the ACE2 expressed in all 72 tissues of humans except red blood cells. According to them highest expression was noticed in male genital organs, cardiovascular and renal tissues and in all portions of gastrointestinal lining predominantly in ilium.[13] Whereas Li et al., addressed ACE2 expression profile in many human tissues, they divided the results according to sex and age groups (Average age 49 years) in order to better investigate the prognosis of COVID-19. In this study, they selected 31 different human organs, and found that ACE2 expression level was highest in small intestine, moderate in lungs epithelia and lowest in blood. Furthermore Li et al., has showed that there is positive correlation between the ACE2 expression levels and immune signatures of both genders (male/ female).[14]

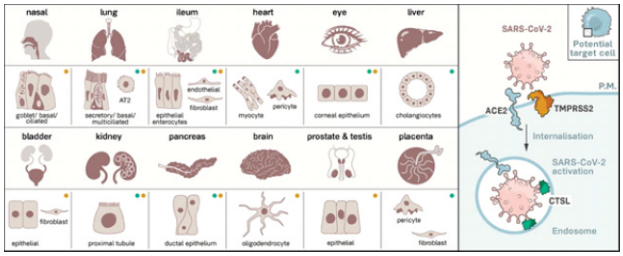

Fig 1: ACE2 expression in various human tissues

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As novel SARS-CoV-2 born COVID-19 epidemic is often symptomatic disease with prevalent symptom of difficulty in breathing, hence expression of ACE2 gene is frequently explored in lung in several studies. Epithelial lining of the nose (i.e., ciliated and goblet cells) and alveolar epithelial type II cells display significant expression of ACE2 along with the TMPRSS2 gene expression, thus clarifying the distinct susceptibility (and vulnerability) of pulmonary cells to be infected by SARS-CoV-2.[15] Interestingly, Xu et al., revealed that ACE2 expression is also observed on mucosal lining (epithelial cells of tongue) of oral cavity.[16] It is also explained that lymphocyte injury leading to lymphopenia observed during the course of COVID-19 is related to ACE2 gene expression in lymphocytes which gives reasonable clue for the significant role of ACE2 expression during COVID-19.[17]

To determine the ACE2 related pathophysiology, Lippi et al, studied the genetic polymorphisms of ACE2 gene in multiple RNA-seq datasets with precise focus on respiratory tree acquired from various human tissues of healthy donors. Similar to previous findings, ACE2 expression was noticed significantly

high in alveolar epithelium, esophagus, liver, kidney, heart, ileum, colon, gall bladder, testis and cornea, which supports the hypothesis of direct infection of these organs by SARS-CoV-2.[18] These findings also explain the occurrence of pyroptosis and diffuse endothelium inflammation as the outcome of ACE2 expression which may ends up with developing thrombotic events during COVID-19.[19]

The highest expression of ACE2 mRNA and protein in testes has exposed the possibility of relationship of male infertility with severe COVID-19. Higher expression of ACE2 mRNA is reported in Sertoli cells, Leydig cells, spermatogonia and seminiferous duct cells of testes[20,21,22] and may support the possibility of COVID-19 mediated male gonadal functions impairment. There are contradictory reports which suggest that COVID-19 infection in males leads to acute phase hypogonadism and reduced androgenic actions which may lead to certain fatal consequences.

There are certain etio-pathogenic hypotheses that are put forward to explain the comorbidities in COVID-19 including indirect inflammatory/immune response resulting in increased pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) levels; disruption of hormonal pathways; increased psychological oxidative stress caused by COVID-19 infection and treatment with antiviral drugs like ribavirin.[23,24]

There are many uncertainties related to COVID-19 prognosis and severity.[25] ACE2 expression profile alone is not sufficient to describe SARS-CoV-2 pathogenesis, however various recent reports have confirmed ACE2 as only possible entrance for novel corona virus.[26,27,28,29,30,31,32] Its expression at different tissues, extends the infection to other sites , resulting in COVID-19 comorbidities as shown in Table 1 including hypertension, gastrointestinal injury, renal failure, pulmonary injury/ inflammation, male infertility, cardiac injury/ arrest and new onset diabetes

Conclusion

This review identified the target sites of SARS-CoV-2 to better understand its pathophysiology and severity and susceptibility to different age groups, genders and races. We focused on only few disorders related to ACE2 expression but still it gives important clues regarding expression pattern of the ACE-2 gene regulating the diversity in immune response. This study not only open the gateway to explore genetic benchmarks contributing in COVID-19 pathogenesis but also designate clinical values of ACE2 gene as potential therapeutic target for designing drugs/ vaccines against novel corona virus. The follow-up studies are needed based on these theoretical explanations to find the possible link between COVID-19 infection and its related comorbidities.

Table 1: Comorbidities related to multi-organ ACE2 expression in COVID-19 patients

ACE2 expression in different Organs	Pathophysiology	References
Blood vessels	Hypertension	33
Small intestine, Duodenum	Gastrointestinal injury	34
Kidney	Renal cancer, renal failure	34
Liver	Liver cancer	35
Lungs	Pulmonary injury/ inflammation	36
Testes	Male infertility	37
Heart	Cardiac injury/ arrest	38
Gall bladder/ Pancreas	Gastrointestinal injury, Diabetes	39
Breast cells	Breast Cancer	40

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