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Review

Correlation between ABO Histo Blood Groups and Covid-19 Susceptibility and Outcome

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Abstract

Since the onset of the Covid 19 pandemic, a disease caused by the virus SARS-CoV-2, research has connected ABO histo-blood group antigens and their role in susceptibility, outcome, mortality, and viral uptake of infected particles. Sample populations studied showed decreased susceptibility and mortality in patients of the O negative blood type. Research is still underway to determine ABO polymorphism and its role in susceptibility and outcome of the disease. Research conducted with SARS-CoV-1disease manifestation has paved the way for proposed mechanisms in which ABO polymorphism was established to affect susceptibility and outcome. The host range of Covid-19 is determined by its Spike protein. Anti-A or Anti-B antibodies from the ABO blood groups bind to the S protein, blocking its connection with angiotensin-converting enzyme 2. ACE2 is the host receptor for SARS and Covid-19. This supports the idea that binding could decrease susceptibility to Covid-19. The S proteins subunit's essential role in receptor binding has become a key research focus in antiviral therapeutic development. Research studying the mechanical mechanism of viral uptake of SARS-CoV-1 and statistical analysis of groups infected with Covid-19 indicates a correlation between ABO histo blood groups and susceptibility and outcome.

Introduction

Correlation between ABO histo-blood group antigens and increased susceptibility and illness in infectious disease has been identified in adenocarcinoma,[1] thrombosis,[2] and esophageal carcinoma.[3] The outbreak of Covid-19 in December 2019 resulted in a 2% mortality rate and an overall hospitalization rate of 2.1%.[4 5] This reached a peak of 9.2% for those over 60.[6] Through membrane microdomains[7], blood group antigens facilitate intracellular uptake of viral particles[8]. Blood types A, B, AB, and O are carbohydrate epitopes present on the surface of red blood cells. Antigenic determinants of blood types A and B are the

trisaccharide moieties GalNAcα1-3-(Fucα1,2)-Galβ- and Galα1-3-(Fucα1,2)-Galβ-, while O blood antigen is GalNAα1,2-Galβ-.[9] Research on the correlation between ABO histo-blood groups and SARS-CoV has led scientists to research the molecular mechanisms of blood antigens present in Covid-19 because of its similarity to SARS-CoV in respect to ACE2.[10]

Blood Type Susceptibility and Mortality

Multiple studies have been conducted spanning different populations researching the correlation between blood group antigens and susceptibility to Covid-19, many of which have proved a correlation present. The largest study conducted to date was in Ontario, Canada. Infection was determined by viral RNA polymerase chain reaction testing, with the second outcome of severe illness or death. They studied a sample population of 225,556 people possessing a mean age of 54. The adjusted relative risk for O blood antigen group in respect to blood antigen groups A, B, AB, was 0.88 (95% Cl, 0.84 to 0.92; absolute risk difference, -3.9 per 1000 [Cl, -5.4 to -2.15]).[11] Rhesus negative antigens in regard to Covid-19 was adjusted relative risk 0.79 [Cl, 0.73 to 0.85]; absolute risk difference, -6.8 per 1000 [Cl, -8.9 to -4.7]. Those that were O negative showed an increased protective response of adjusted relative risk, 0.74 [Cl, 0.66 to 0.83]; absolute risk difference, -8.2 per 1000 [Cl, -10.8 to -5.3]. These results show a direct association between O and Rh-negative blood groups and lower susceptibility to infection of Covid-19.[12]

In China, research conducted by Jiao Zhao studied the correlation between blood type susceptibility and mortality in a sample population of 1,775 patients. The patients had a blood type distribution of A, B, AB, and O of 37.8%, 26.4%, 10%, and 25.8%. The proportion of blood group A among the patients positive for Covid-19 was higher in the control group, with 37.8% in the former versus 32.2% in the latter $p<0.001$). Those in the O blood group were lower than the control group, 25.80% versus 33.84% ($P<0.001$). Covid-19 susceptibility increased for blood group A (odd ratio 1.279, 95% Cl 1.136~1.440) and decreased for blood group O (odds ratio 0.680, 95% Cl 0.599~0.771).[13]

Researchers applied this distribution pattern in studying increased risk for deceased patients. The distribution for blood groups A, B, AB, and O in a sample of 206

deceased patients was 41.3%, 24.3%, 9.2%, and 25.2%. Lower risk of death was associated with blood group O versus non-O groups, with an odds ratio of 0.660 (95% Cl 0.479~0.911, P=0.014). Blood group A was associated with a higher risk of death versus non- A groups with an odds ratio of 1.482 (95% Cl 1.113 ~1.972, P = 0.008).[14]

Covid-19

These studies propose a trend in the correlation between ABO blood groups and the severity of Covid-19. However, research is still underway on the molecular mechanism by which ABO polymorphism plays a role in susceptibility and severity. Research conducted connecting ABO blood groups, and SARS-CoV-1 has paved the way for studies concerning Covid-19 and the molecular mechanism by which antigens play a role in susceptibility and outcome. Severe acute respiratory syndrome, also known as SARS, was first recognized in Guangdong Province, China, in November 2002.[15] In June 2003, the epidemic was finally contained,[16] possessing a case fatality rate of 11%.[17]

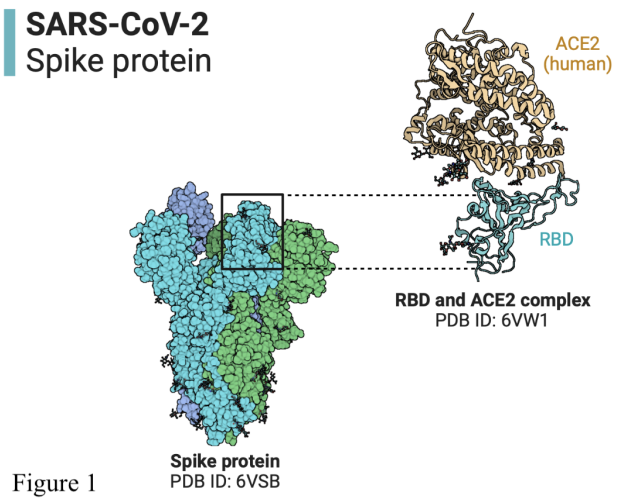

Figure 1

Spike Proteins and ACE2

ABH antigens present themselves on platelets from a person with the corresponding phenotype.[18] They are found on epithelial cells, commonly in the upper respiratory tract, nasal epithelium, and trachea.[13] These cells can synthesize ABH carbohydrate epitopes. The host range of Coronavirus is determined by its S protein (Aka spike protein) (Figure 1).[19] S proteins are type I transmembrane and class I fusion proteins possessing an N-terminal domain and receptor binding domain, making up the S1 subunit, C-terminal domain, fusion peptide, heptapeptide repeat sequence 1, HR2, TM domain, and cytoplasmic domain, making up the S2 subunit.[20] These domains function for receptor binding and virus-cell fusion (Figure 2).[21] Because of their nature, researchers proposed in a study that the S

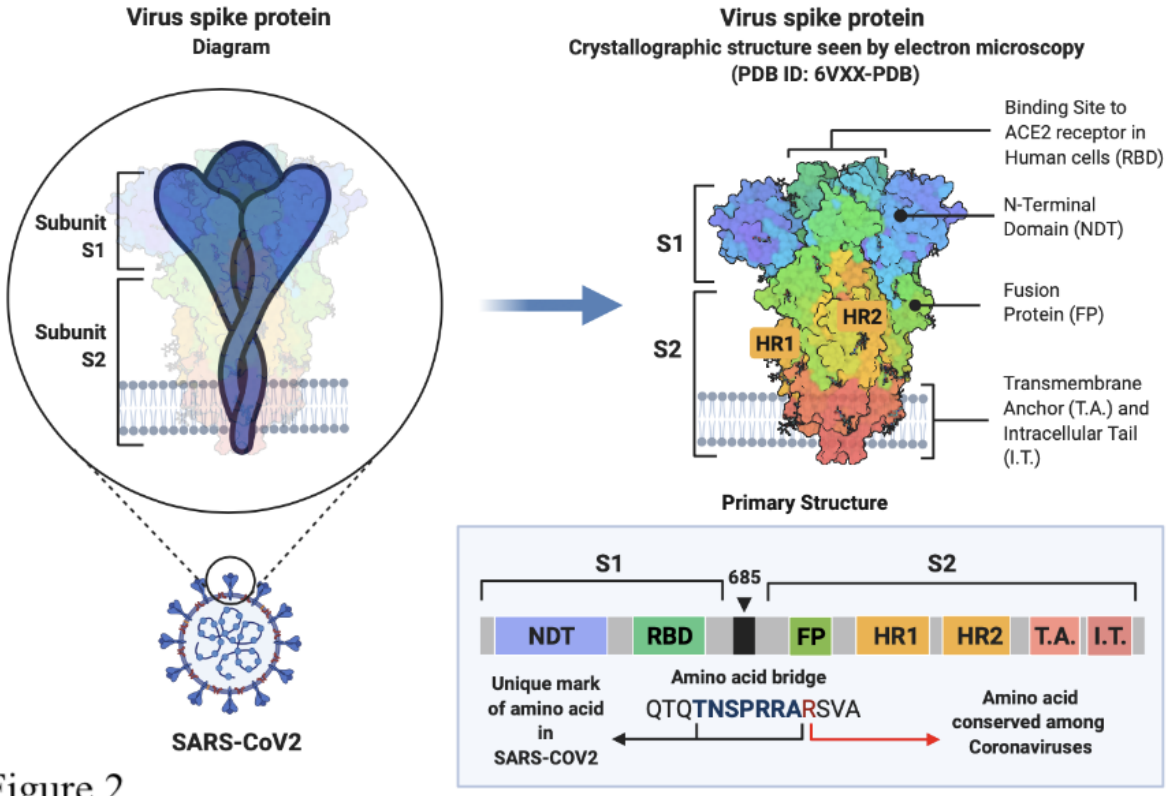

Figure 2

"An In-Depth Look into the Structure of the SARS CoV2 Spike Glycoprotein", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

protein of virions produced by either A or B blood groups would be able to be decorated with A and B carbohydrate epitopes. The anti-A or anti-B antibodies from the ABO blood groups could bind to the S protein and block its connection with angiotensin-converting enzyme 2 (ACE2). Since ACE2 is the host receptor for SARS-CoV-1,[22], inhibiting the binding could decrease susceptibility to SARS-CoV-1. This hypothesis was tested using a cell binding assay that reconstructed the interactions between S proteins and ACE2.[23] It was indicated that the interaction between the S proteins and ACE2 could intervene in adhesion between ACE2 and cells possessing S proteins and A histo-blood groups. This would be inhibited by anti-A-antibodies, reducing susceptibility.

Cell adhesion is used to screen molecules that block the transfusion of a virus without the use of infected molecules. This method displayed monoclonal anti-A antibody or natural plasma anti-A inhibiting SARS-CoV S proteins bonding to ACE2.[10] Correlating studies confirmed groups of glycosylation sites are located around the RBM of the SARS-CoV S protein.[24 25]

Antibodies can bind to these glycans and inhibit the interactions between ACE2 and S proteins by interfering with their viral replication cycle.[26] This block decreases susceptibility to SARS-CoV. These studies support the idea that ABO-histo-blood group antigens, through the actions of natural antibodies, could inhibit the transfusion of infectious particles, causing complement-mediated-neutralization.[27] [10]

SARS-CoV-1 Blood Type and Susceptibility

During the outbreak of SARS-CoV-1, a study conducted in Hong Kong, China, modeled the effect of natural anti-A and B antibodies and the susceptibility of the virus. Three transmission patterns, each possessing different transmission probabilities, according to the amount of protection provided by anti-histo-blood group natural antibodies presented themselves. The stronger the group effect, the more protection offered. Researchers assessed group effect based on a population of infected individuals possessing different blood type frequencies—the more substantial the impact of the group, the stronger the delay of the epidemic. Results displayed a strong group effect in groups with high frequencies of blood type O. To confirm the results, they ran simulations consisting of A, B, and AB blood groups, and the results were unmodified.[28] This study shows mathematical evidence supporting ABO histo-blood groups' contribution to viral transmission in SARS-CoV-1.

"ABO-histo-blood group antigens, through the actions of natural antibodies, could inhibit the transfusion of infectious particles, causing complement-mediated-neutralization."

Heptad Repeat Domain Dependency

This research conducted on S proteins and their role in severe respiratory syndrome has led to correlating studies and clinical research into antiviral drug development for Covid-19 and its illness caused by it, Covid 19. The S protein, and its subunits, S1 and S2, play an essential role in receptor binding and entry of infectious viral particles into its host cell (Figure 3), making it an important focus of research into producing antiviral medication.

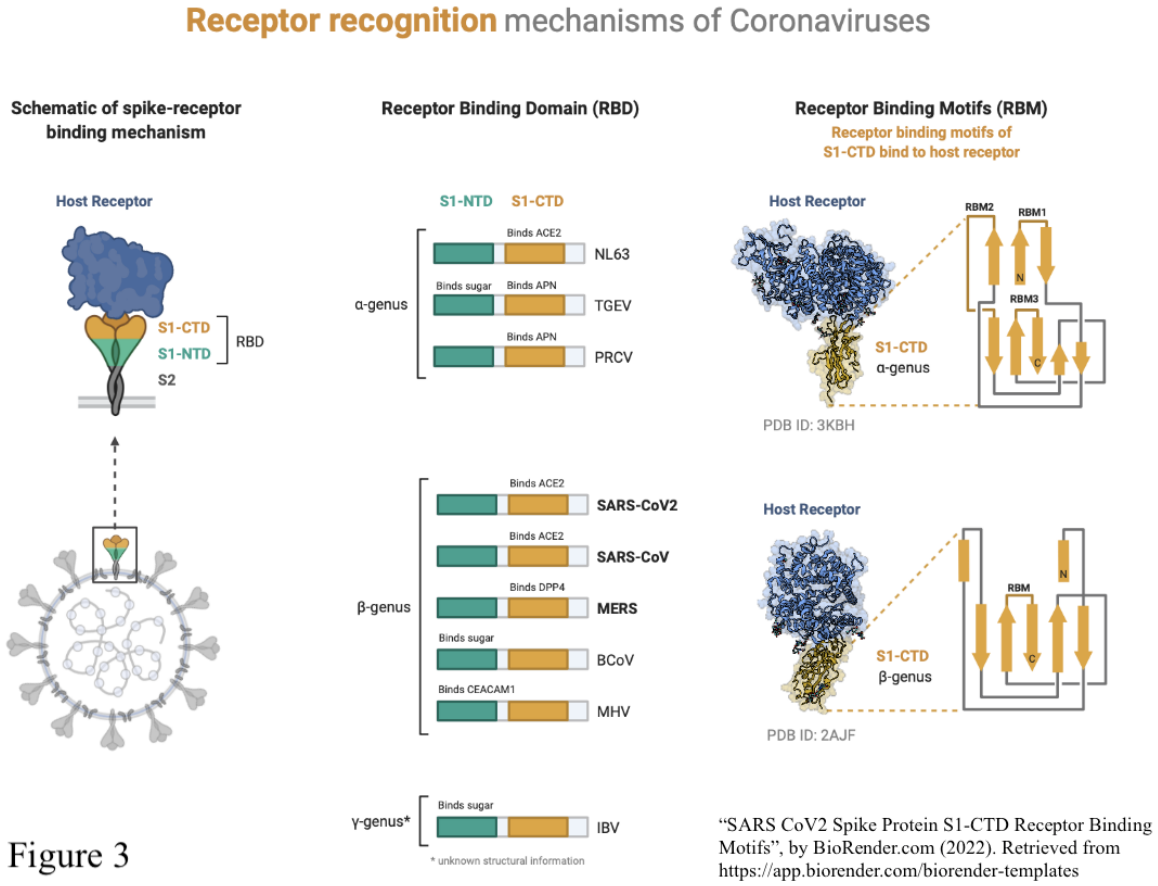

Figure 3

"SARS CoV2 Spike Protein S1-CTD Receptor Binding Motifs", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

In the S2 subunit, the heptad repeat domain has been a critical focus in research for antiviral therapeutic medication. The heptad repeat area in the S2 subunit plays a crucial role in HCV infection. As a mode of interaction for HR1 and HR2.[29] In a similar study, a synthetic peptide created from the stem region of a Zika virus envelope protein inhibits the infection and other flaviviruses in vitro, disrupting the integrity of the viral membrane.[30] This study indicates higher antiviral efficiency when peptides taken from conserved regions of viral proteins are utilized in developing the treatment. A study further testing this theory found that peptides are taken from the HR2 part of the S2 subunit formed class 1 viral fusion proteins of enveloped viruses competitively bound to viral HR1, resulting in an inhibition of infection mechanisms.[31] This opens the door for developing a therapeutic drug that works as a fusion inhibitor to treat Covid-19 (Figure 4).[32] Clinical trials are currently underway researching the dependency of Covid-19 on the S protein.[33] [34] [35]

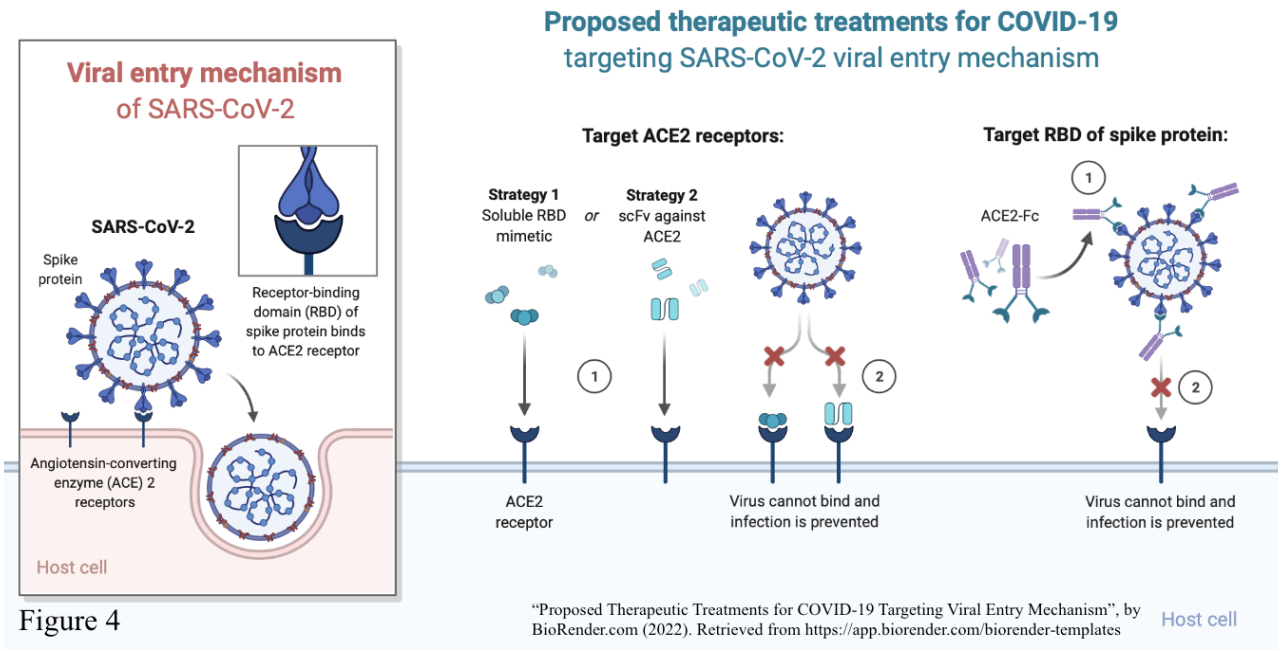

Figure 4

"Proposed Therapeutic Treatments for COVID-19 Targeting Viral Entry Mechanism", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates

Conclusion

The correlation between S proteins and ABO histo-blood groups supports the theory that blood type plays a role in susceptibility and outcome regarding Covid-19. Statistical analysis of infected and noninfected populations show a correlation between blood type O- and a decrease in susceptibility and mortality rate of infected individuals. Blood type O displayed an odds ratio of 0.680, 95% Cl 0.599~0.771 regarding susceptibility and an odds ratio of 0.660 (95% Cl 0.479~0.911, P=0.014) regarding mortality of infected individuals. As research continues to further the understanding of the mechanisms of infection, better therapeutic antiviral medications for individuals exposed will become a reality, combating the mortality rate and susceptibility of Covid-19.

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