Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The influence of ABO blood groups on COVID-19 susceptibility and severity: A molecular hypothesis based on carbohydrate-carbohydrate interactions

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ABSTRACT

The world is experiencing one of the most difficult moments in history with the COVID-19 pandemic, a disease caused by SARS-CoV-2, a new type of coronavirus. Virus infectivity is mediated by the binding of Spike transmembrane glycoprotein to specific protein receptors present on cell host surface. Spike is a homotrimer that emerges from the virion, each monomer containing two subunits named S1 and S2, which are related to cell recognition and membrane fusion, respectively. S1 is subdivided in domains S1A (or NTD) and S1B (or RBD), with experimental and *in silico* studies suggesting that the former binds to sialic acid-containing glycoproteins, such as CD147, whereas the latter binds to ACE2 receptor. Recent findings indicate that the ABO blood system modulates susceptibility and progression of infection, with type-A individuals being more susceptible to infection and/or manifestation of a severe condition. Seeking to understand the molecular mechanisms underlying this susceptibility, we carried out an extensive bibliographic survey on the subject. Based on this survey, we hypothesize that the correlation between the ABO blood system and susceptibility to SARS-CoV-2 infection can be presumably explained by the modulation of sialic acid-containing receptors distribution on host cell surface induced by ABO antigens through carbohydrate-carbohydrate interactions, which could maximize or minimize the virus Spike protein binding to the host cell. This model could explain previous sparse observations on the molecular mechanism of infection and can direct future research to better understand of COVID-19 pathophysiology.

Introduction

In December 2019, a new type of coronavirus was discovered in Wuhan province, China, causing a condition of severe respiratory failure called COVID-19. SARS-CoV-2, the technical name of this new infectious agent, is genetically linked to SARS-CoV-1 and MERS-CoV, two other human coronaviruses that have caused severe lower respiratory tract infections in China in 2002–2003 and in the Middle East since 2012, respectively [1]. From China, SARS-Cov-2 quickly spread across the world, making the World Health Organization (WHO) decree this pathology a pandemic in mid-March 2020 (https://www.who.int/dg/speeches). As of the 13th July 2020, more than 13 million cases had been registered worldwide, with about 570,000 reported deaths (https://www.worldometers.info/coronavirus/).

The rapid transmissibility of SARS-CoV-2 has led several countries to adopt strategies to mitigate contagion spread, which includes social isolation/distancing, lockdown and temporary closure of educational institutions [2,3]. Such measures aim to prevent an accumulation of a large number of people with the severe form of the disease in need of hospital care simultaneously, which could lead to a collapse in health systems worldwide [4]. However, the great concern and need for such governmental policies has led part of the affected nations to an unprecedented economic and social crisis, since unemployment rates, the number of companies' bankruptcies and reports of depressive conditions and other mental disorders have greatly increased in this period [5–8].

In this context, the global scientific community has engaged in a worldwide effort to understand the pathophysiology of COVID-19, in order to develop an effective treatment as quickly as possible. Results obtained so far have proved this journey very fruitful. For instance, it has been demonstrated that although SARS-CoV-2 is directly related to respiratory tract dysfunction due to an intense inflammatory process called “cytokine storm”, which promotes the accumulation of fluid in alveoli [9], the infection can also be systemic, with evidence of the

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presence of viral genetic material in the gastrointestinal tract and the central nervous system [10,11]. These findings can potentially explain why symptoms unrelated to the respiratory tract, like vomiting and diarrhea [12], as well as neurological disorders [13], are found in COVID-19 patients.

Studies developed so far have also started to shed a light on the molecular mechanisms mediating the process of viral infection in human cells. The entry of viral particles in host cells depends on the specific binding of virus Spike protein to the human membrane receptor ACE2 - from Angiotensin-Convertor Enzyme 2 [14,15]. This receptor is distributed all over the surface of a large diversity of cell types, such as those from the central nervous system, upper airways and lungs, liver, kidneys, pancreas, heart and endothelial cells [16]. Its function is equally diverse depending on the cell type where it lies, ranging from blood pressure regulation, through the renin-angiotensin-aldosterone system, to controlling blood glucose and renal activity [17,18]. Despite the central role of ACE2 in the virus-human cell interaction, other host molecules have also been recognized as important players in the infectious process, such as the transmembrane proteins CD147 [19,20] and TMPRSS2 [21].

CD147 (also known as EMMPRIN, from Extracellular Matrix Metalloproteinase Inducer, basigin, M6, neurothelin and HAb18G) is believed to function as a coreceptor for the novel coronavirus attachment to host cells [20]. It is a type I transmembrane protein heavily glycosylated that plays roles in spermatogenesis and fertilization, neural network formation and development, tumor metastasis and angiogenesis, and cardiovascular disease [22,23]. In turn, TMPRSS2 (from Transmembrane Protease Serine type 2) has been reported to promote cleavage of Spike protein in two different sites to induce SARS-CoV-1 and SARS-CoV-2 invasion [24–26], since application of a clinically available inhibitor of its protease activity blocks SARS-CoV-2 entry in cell culture [21]. TMPRSS2 is lightly glycosylated, playing important roles in human and mammal development and homeostasis, as well as in several diseases, such as cancer [27] and infecton by influenza [28].

A couple of preprint reports and a study using large-scale genetic data from infected and non-infected patients have identified a significant association between type A blood individuals (from the ABO blood system) and higher susceptibility to both infection with SARS-CoV-2 and development of more severe forms of COVID-19 [29–31]. Although a correlation between ABO blood type and infection susceptibility is not unique of the new coronavirus, since it was previously reported also for the infection by the protozoan that causes malaria [32–34], the molecular mechanism underlying this relationship is still poorly understood.

Hypothesis

Supported by an extensive bibliographic review highlighting (i) the mode of binding of SARS-CoV-2 to cell receptors, as well as (ii) the biochemical aspects of ABO blood group system and its association to infection and some circulatory conditions, we hypothesize that the influence of blood type on COVID-19 severity relies on the differential clustering of glycoproteins receptors to SARS-CoV-2 on host cell surface, induced by ABH antigens through carbohydrate-carbohydrate interactions with the glycan portions of these receptors, which could modulate virus binding to the target cell.

Supporting evidence of the hypothesis

SARS-CoV-2 binding to host cells

Although SARS-CoV-2 is a new virus, much has been studied about its biochemical characteristics, especially regarding its Spike protein, within less than a year since its discovery [35–38]. In this way, because our focus is on trying to understand how an individual's blood type turns him more or less susceptible to being infected, it is important to address the main known aspects of the virus-host cell interaction.

From the pathogen perspective, the interaction is mediated by Spike (S) – a structural glycoprotein that emerges from the viral envelope in a homotrimeric arrangement, i.e., through the non-covalent association of three equal monomers or polypeptide chains. Each monomer is composed of two subunits called S1 and S2, which are essential for the binding of the virus to receptors present on host cells surface and for the fusion of the viral coat with the plasma membrane, respectively. The two subunits are connected by an amino acid segment that in some coronaviruses species, including SARS-CoV-2, is cleaved by TMPRSS2 at a stage prior to the membrane fusion [39]. However, it is suggested that the high pathogenicity of the novel coronavirus is attributed to the additional Spike protein priming by furin, a specialized serine endoprotease that cleaves multibasic motifs, a peculiar characteristic not seen in any coronavirus species up to date [40,41].

S1 is subdivided into two domains named S1A (or S^A) and S1B (or S^B), arranged in a “V” conformation. The former corresponds to the N-terminal region of the polypeptide chain (hereafter called NTD, from N-Terminal Domain) and, in most coronaviruses, interacts with glycoproteins and glycolipids that have sialic acid molecules at the distal end of the glycan portion, especially if the monosaccharide is in the modified form of 5-N-acetyl-9-O-acetyl-sialoside [42]. S1B (hereafter named RBD - from Receptor-Binding Domain), on the other hand, binds to the ACE2 receptor, which is largely recognized as the main entry route for some coronaviruses into host cells [37]. For other coronaviruses, instead, this function is played by diptidyl-peptidase 4 - DPP4 [43,44] or aminopeptidase N – APN [45,46] receptors.

In some coronaviruses species, like MERS-CoV, the likelihood interaction of its RBD domain to DPP4 receptor seems to be increased by prior binding of NTD domain to sialosides [47,48]. For most coronaviruses, however, it is not known if both domains are used for viral entry [49,50], altought studies from others mammalian coronaviruses indicate that sialosides may facilitate the interaction between Spike protein and transmembrane receptors, and can be even essential in more advanced stages of infection [51,52], suggesting that both domains are equally necessary for virus attachment, entry and spread.

Interestingly, it is reported that SARS-CoV-1 does not bind sialic acid, a feature that could be extended to the novel coronavirus [53]. In fact, a recent preprint study using glycan microarray did not detect significant fluorescent signals when SARS-CoV-2 Spike protein was incubated with sialic acid-containing oligosaccharides [54]. However, *in silico* preprint analyses through molecular docking simulations and electronic density mapping surface predict the existence of a sialic acid-binding site in SARS-CoV-2 NTD domain similar to that one in MERS-CoV [55,56]. Surprisingly, sialoside moieties are present in glycans attached to both ACE2 [57] and CD147 [58] receptors, which are potentially necessary for the virus anchoring to host cells [59].

Taken together, these conflictant reports urge more deeply studies to clarify the sialoside participation in SARS-CoV-2 infectivity and pathogenicity.

Biochemistry of ABO blood system

Discovered by Karl Landsteiner at the beginning of the 20th century [60], the ABO system is still considered the most important type of blood group classification in clinical transfusion medicine nowadays. Their characteristic epitopes are produced by the coordinated action of at least two independent loci [61]: FUT1, that is located on chromosome 19 and encodes the enzyme α-2-L-fucosyltransferase, and the ABO locus, which encodes the enzymes α1 → 3-N-acetyl-galactosaminyltransferase (enzyme A) and α1 → 3-galactosyltransferase (enzyme B), and is located in the terminal portion of the long arm of chromosome 9.

The translated product of FUT1 recognizes and adds an L-fucose residue to the terminal disaccharide of a glycan precursor anchored to lipids or proteins on cell surface [62]. The disaccharide is formed by a terminal galactose residue connected to an N-acetylglucosamine

molecule, either through a β3 or β4 glycosidic bond. Addition of L-fucose to galactose creates the antigen H, the chemical determinant of the O phenotype [62]. Antigens A and B, on the other hand, arise from enzymatic modification of the H epitope through the attachment of the D isomer of N-acetylgalactosamine or galactose to the terminal galactosil residue, which is mediated by enzymes A and B, respectively. The AB phenotype arises from the simultaneous expression of the two transferases, promoting the formation of their respective antigens in the same cell [62].

ABH antigens are not restricted to the erythrocyte membrane, being found in a wide variety of other cells such as lymphocytes, platelets, venular and arterial capillary endothelium, spleen sinusoid cells, bone marrow, gastric mucosa, in addition to secretions and other fluids such as saliva, urine and milk [63], a feature involved with numerous physiological and pathological processes, as discussed below.

ABO blood system relationship to infections and other pathological conditions

Individuals with certain types of ABO blood groups are more susceptible to diverse kinds of infections [64]. For instance, blood types A and AB predisposes individuals to severe malaria, while type O confers resistance to the protozoan agent. Additionally, this blood system is directly or indirectly associated to some cardiovascular conditions. Groot et al [65] observed that type A individuals are more likely to have an unhealthier aging than those bearing the O phenotype. These authors also reported that people with A, B and AB blood types are more likely to develop thrombosis and myocardial infarction, while those with type O are more likely to develop hypertensive conditions. The A antigen also seems to predispose individuals to a greater risk of thromboembolism and metabolic disorders, such as hyperlipidemia, hypercholesterolemia and diabetes mellitus [66].

The mechanisms involved in these relationships are, however, poorly understood, with speculative explanations offered to most cases, whereas solid explanations are rare. For malaria infection, for example, it has been reported that type A blood induces rosette formation of erythrocytes, a known virulence factor and contributor to microvascular ischemia and thrombosis [65]. For cardiovascular effects, it is suggested that individuals carrying the A antigen have a higher prevalence of thromboembolism due its association with high levels of von Willebrand factor [67], a glycoprotein synthesized and secreted by endothelial cells and megakaryocytes that stimulates coagulation [68]. In this particular case, it is speculated that antigen A, as well as B, act by increasing the secretion of the factor or by decreasing its clearance, or both [66].

These explanations, however, do not take into account a molecular perspective for the ABO blood group participation in the pathological conditions discussed. In other words, they do not respond the question “how exactly do ABH antigens correlate with infection and cardiovascular pathophysiology?”.

A more detailed answer can be found in a work carried out in 2009 by Cohen, Hurtado-Ziola and Varki [69]. Using three proteins that specifically bind to sialosides, the group analyzed the pattern of interaction between these molecules and human erythrocytes representing the four ABO blood phenotypes. They observed that proteins interacted more strongly with A, B and AB cell types, with a certain preference for the first, and less with the O cell type. When using specific glycosidases that converted determinants A and B to H, they found that interactions between all three proteins included in the study and their sialoside ligands decreased to the levels observed for the original type O red blood cells. To explain these findings, the authors proposed a model where blood antigens modulate the distribution of sialosides in the plasma membrane, with antigens A and B (specially the former) stimulating the formation of carbohydrate clusters, whereas the H antigen would not promote such effect. The mechanistic causal explanation to these observations was attributed to the presence of carbohydrate-carbohydrate interactions (CCIs) between ABO blood determinants and sialic acid-containing glycans, which could influence, even indirectly, cell recognition and communication [70,71]. CCIs can occur in *cis*, when the interacting carbohydrates are anchored on the same cell, or in *trans*, when they are anchored on different cells [69].

CCIs have been reported since 1963, when Humphreys [72] demonstrated the participation of proteoglycans in cell adhesion of marine sponge. Since then, other studies have supported these findings, showing that self-association of surface carbohydrates guides cell aggregation in marine sponge and mouse embryo [73–75]. The first two decades of the 21st century have been characterized by great advances on this subject, specially concerning methodological developments for studying CCIs [76–82], as well as by showing their participation in antibody-receptor binding [83], neonatal immunity stimulation [84], oncogenesis [85] and potential application in drug delivery approaches [86].

Interestingly, divalent ions, mainly Ca^{2+}, seem to be very important to promote CCIs. Several studies have showed that this kind of interaction only occur in the presence of these ions [87–90], possibly because they coordinate forces to mediate interactions, although ionic forces could also be involved [91].

Consequences of the hypothesis and discussion

It is in light of this whole picture that we formulate the hypothesis that the ABO blood system correlates to COVID-19 severity due to CCIs. We speculate that the antigens that determine A, B, AB and O blood cell phenotypes can modulate the distribution of sialic acid-containing receptors in the plasma membrane of host cells. Specifically, we hypothesize that mostly antigen A, but also antigens B and AB at a lesser extent, can stimulate the formation of sialoside clusters in target cells through *cis* CCIs. This would maximize the interaction of the cells with SARS-CoV-2 by increasing the likelihood of binding of the NTD and (possibly) RBD domains to CD147 and ACE2 receptors, respectively, through multivalency and avidity. The participation of RBD is proposed based on a recent preprint report showing that ACE2 is also decorated with sialoside glycans [57]. Additionally, *trans* CCIs cannot be neglected, since Spike can be decorated with glycans from host cells [92]. In this case, natural or monoclonal anti-histo-blood group antibodies could bind to Spike glycans, inhibiting its interaction to host cell glycoprotein receptors, as reported previously for SARS-CoV-1 [93] and recently proposed for SARS-CoV-2 [94].

It is important to note that a recent preprint study reporting the inability to detect the interaction between the novel coronavirus Spike protein and sialic acid through glycan microarray [54] does not argues against the proposed model of *trans* CCI, since it is based on the modulation of the distribution of sialoside-containing receptors in plasma membrane. In this perspective, even the possibility of occurrance of *trans* CCIs in the reported assay presumably would not induce detectable fluorescent signals due the immobilization of the tested glycans on the array chip, therefore not allowing the formation of carbohydrate clusters, which would accordingly increase the Spike binding.

The present hypothesis becomes more interesting when we take into account that (i) COVID-19 increases the risk of coagulopathies and venous thromboembolism in those patients who develop a severe condition [95] and (ii) a recent proposition that these traits can be related to deregulatory balance of von Willebrand factor levels [96]: two features more prevalent in individuals with type A blood, as mentioned early.

A last point to be addressed is that some reports have proposed the use of zinc as a coadjuvant component in the treatment of COVID-19 [97,98]. Although a rigid body of evidence for its efficacy is missing, it is suggested that zinc supplementation performs antiviral activity by various mechanisms, such as restoration of depleted immune function, blocking of virus attachment and infection, and inhibition of virus replication [99]. The hypothesis described here can be considered in

future (pre)clinical studies to understand the possible role of this micronutrient in this context. As CCIs are commonly mediated by Ca^{2+}, zinc ions (Zn^{2+}) could disrupt its proposed coordinated forces and consequently break the interactions between ABH antigens and sialoside moieties, blocking or at least diminishing SARS-CoV-2 anchoring to host cells. This idea arises from studies with hydroxyapatite crystals, where substitution of Zn^{2+} for Ca^{2+} cause remarkable rearrangement of the unit cells [100,101]. Extending this observation to our model, it is possible that similar changes also occur in the molecular environment of CCIs.

In summary, this work proposes that the molecular mechanism underlying the influence of ABO blood groups on COVID-19 susceptibility and severity relies on carbohydrate-carbohydrate interactions between ABH antigens and sialoside glycans present on host cell receptors. It is important to highlight that as a review work, its conclusions should be seen and interpreted carefully as an attempt to contribute to a better understand of the pathophysiology of COVID-19, which may be further supported or not with experimental and clinical studies.

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CRediT authorship contribution statement

José Caetano Silva-Filho: Conceptualization, Writing - original draft, Writing - review & editing. **Cynthia Germoglio Farias de Melo:** Writing - original draft. **Janaína Lima de Oliveira:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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