Blood group ABO polymorphism inhibits SARS-CoV-2 infection and affects COVID-19 progression

Fumiichiro Yamamoto,¹ Miyako Yamamoto¹ ét Eduardo Muñiz-Díaz²
¹Laboratory of Immunohematology and Glycobiology, Josep Carreras Leukaemia Research Institute, Badalona, Spain
²Department of Immunohematology, Banc de Sang i Teixits – BST, Barcelona, Spain

The ABO blood group system consists of glycan antigens A and B and polyclonal antibodies against these antigens in individuals who do not express the antigens (Landsteiner’s law). A and B antigens can also be expressed on other types of cells than RBCs, including epithelial cells of the gastrointestinal and respiratory tracts and endothelial cells lining the blood vessels. Therefore, ABO matching is also crucial for cell/tissue/organ transplantation, in addition to RBC transfusion.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the ongoing pandemic of coronavirus disease 2019 (COVID-19). Although most infected people show no or mild symptoms, some progress to severe pneumonia, multiple organ failure and even death [1]. Older people are at high risk [2]. Eighty per cent of deaths have occurred in people with at least one underlying comorbidity, particularly cardiovascular disease/hypertension, overweight/obesity and diabetes. Male patients tend to have a worse prognosis than female patients with a greater risk of being hospitalized in the ICU and subsequent death. SARS-CoV-2 exhibits extensive organotropism, infecting and proliferating in epithelial cells of the respiratory and digestive tracts. An overreaction of the immune system by cytokine storm can attack the tissues and transform COVID-19 into a multi-organ disease.

Similar to the SARS-CoV responsible for SARS, SARS-CoV-2 is encapsulated with a cell membrane. Spike (S) glycoproteins embedded in the membrane mediate viral association with the cell surface receptor, angiotensin-converting enzyme 2 (ACE2). S proteins express A and/or B glycan antigens, reflecting the ABO phenotype of the cells where viruses are produced. In an experimental SARS cell model, the physical interaction between viral S proteins carrying A antigens and cellular ACE2 proteins was inhibited using mouse monoclonal or human polyclonal anti-A antibodies [3]. Similar observations have been made with HIV and measles viruses expressing A or B antigens [4, 5].

Association of ABO blood groups and SARS-CoV-2 infection/COVID-19 disease

The ABO blood group polymorphism was previously shown to influence the susceptibility to SARS with individuals in groups A and O having a higher and lower risk, respectively [6]. Since 11 March 2020, several papers reported the association between ABO blood groups and SARS-CoV-2/COVID-19. These include papers by Zhao, et al. [7], Zietz et al. [8], and Zeng et al. [9], which were initially posted on medRxiv, the preprint server for health sciences. Li, et al. [10] just published an article in Br. J. Hematol. The authors compared ABO blood group distribution among 265 SARS-CoV-2-infected patients and 3,694 healthy controls. The proportion of group A in patients was significantly higher than in healthy controls (39.3% vs. 32.3%, P = 0.017), while the proportion of group O in patients was significantly lower than in healthy controls (25.7% vs. 33.8%, P < 0.01). The distribution proportions of groups A and O within various ages and genders were almost consistent with the trend. A higher and lower infectious risk of group A and O individuals, respectively, was also observed in the other studies [7–9].

On 8 June, the genetic testing company 23andMe released preliminary unpublished data from its ongoing COVID-19 genetic study, using the survey of more than 750,000 participants [11]. The percentage was calculated from individuals with different ABO groups who reported COVID-19: 1.3%, 1.4%, 1.5% and 1.5% for groups O, A, B and AB, respectively, among all participants, and 3.2%, 3.9%, 4.0% and 4.1% among health professionals. The protective effect of group O against acquisition (OR = 0.86, P < 0.0001) and hospitalization (OR = 0.81, P = 0.05) was observed in the entire population and also among health professionals (OR = 0.81, P < 0.0001 to acquire). The results showed the power of this novel approach to study genetic associations based on genome sequencing and survey questions.

Correspondence: Fumiichiro Yamamoto, Josep Carreras Leukaemia Research Institute, Badalona, Catalunya, Spain.
Email: fyamamoto@carrerasresearch.org
Another important advance was achieved in the genome-wide association study (GWAS) published in *N Engl J Med* [12]. The authors analysed 8,582,968 single nucleotide polymorphism (SNP) sites from 835 patients with severe COVID-19 disease defined as respiratory failure and 1,255 control participants from Italy and 775 patients and 950 control participants from Spain. Significant associations were observed with SNPs on chromosome 3p21.31 and on 9q34.2. Furthermore, the frequency of the risk alleles of the lead variants in 3p21.31 and 9q34.2 was higher in patients with mechanical ventilation compared to those who received oxygen supplementation. The association on 9q34.2 was mapped to the ABO locus. The group-specific analysis showed a higher risk for group A (OR = 1.45, \( P = 1.48 \times 10^{-6} \)) and a protective effect for group O (OR = 0.65, \( P = 1.06 \times 10^{-5} \)).

**Natural antibodies against SARS-CoV-2 infection**

The SARS-CoV-2 viruses produced in individuals of groups A, B, AB and O express A, B, A and B antigens, and none, respectively. People in groups A, B, AB and O have anti-B, anti-A, none and anti-A/anti-B/anti-A,B antibodies, respectively. Therefore, these antibodies can react to the corresponding antigens and inhibit, at least partially, interpersonal infection between certain individuals with different ABO phenotypes [13]. This situation resembles ‘matched’ and ‘mismatched’ combinations in blood transfusion. For example, SARS-CoV-2 viruses produced in group A individuals may express A antigens and infect group A or AB individuals without such antigen–antibody reactions. However, infection in group B or O that possess anti-A antibodies may be somewhat inhibited. Similarly, group B SARS-CoV-2 viruses can infect individuals from group B or AB. However, infection in group A or O individuals possessing anti-B antibodies may be somewhat limited. SARS-CoV-2 infectivity is shown schematically in Fig. 1. Solid and dotted arrows indicate infectivity without and with inhibition, respectively. Once infection is established, newly produced SARS-CoV-2 viruses exhibit the same ABO phenotype as the infected individual, and these antibodies no longer inactivate them. Therefore, natural antibodies seem to be only relevant for the initial attack rate and not for the subsequent productive infection. Ironically, group O individuals with the lowest risk of becoming infected by SARS-CoV-2 can produce group O SARS-CoV-2 viruses capable of infecting individuals with any ABO phenotype efficiently. Consequently, countries with the highest frequency of O alleles, such as Ecuador (75%) and Peru (70%), also suffer from the COVID-19 pandemic. It should be noted that infectivity is directional and depends on matched/mismatched ABO phenotypes of SARS-CoV-2 and host cells.

Individuals with anti-A antibodies (groups O and B combined) were represented less in patients with COVID-19 than individuals lacking anti-A antibodies (groups A and AB combined) [14]. Furthermore, patients in group O were underrepresented, whereas group B patients were overrepresented, suggesting a greater protective effect of anti-A antibodies in group O than anti-A antibodies in group B (\( P < 0.001 \)). Anti-A, anti-B and/or anti-A,B antibodies of the IgA class may be primarily responsible for mucosal immunity, although natural antibodies of other classes, especially of the IgG class, may also function. Inhibition results in a decrease of R₀, the expected number of cases generated directly by a case. Furthermore, inhibition may be more effective in ABO-heterogeneous populations than in ABO-homogeneous populations.

Group O individuals have 25% lower serum levels of von Willebrand factor (vWF) and factor VIII (FVIII) essential for platelet adhesion, aggregation and fibrin clot formation. vWF, a transporter and stabilizer protein for **Fig. 1** Differential inhibition of infection between SARS-CoV-2 viruses exhibiting different ABO phenotypes and individuals of groups A, B, AB and O.
FVIII, is mostly synthesized in vascular endothelial cells and released into plasma. Group non-O individuals have an increased risk of thrombosis, pulmonary embolism and venous thromboembolism [15]. The dysregulation of vascular tone and permeability and the induction of cytokine storm and redox stress are therefore somehow associated with the ABO polymorphism. Consequently, the ABO polymorphism can differentially affect the progression of COVID-19 disease by the molecular mechanism that does not involve natural antibodies. However, the disease progression also depends on other more underlying relevant factors. And several of them have much higher ORs than the ABO polymorphism. For example, people over the age of 85 have ORs of 13 and 630 for hospitalization and death, respectively, compared to people between 18 and 29 [2]. In these circumstances, the ABO effects on clinical outcomes of severity and mortality can be easily masked, which may provide an explanation for the controversy about the presence/absence of association [16, 17]. The new studies that are coming will help us to better clarify this and many other aspects of the ABO involvement in the SARS-CoV-2 infection and the COVID-19 progression.

References

1 Huang C, Wang Y, Li X, et al.: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506
2 Centers for Disease Control and Prevention (CDC): Coronavirus Disease 2019 (COVID-19), People at Increased Risk for Severe Illness. Available online: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html [accessed on 20 August 2020].
3 Guillón P, Clément M, Séhille V, et al.: Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 2008; 18:1085–1093
4 Arendrup M, Hansen JE, Clausen H, et al.: Antibody to histo-blood group A antigen neutralizes HIV produced by lymphocytes from blood group A donors but not from blood group B or O donors. AIDS 1991; 5:441–444
5 Preece AF, Strahan KM, Devitt J, et al.: Expression of ABO or related antigenic carbohydrates on viral envelopes leads to neutralization in the presence of serum containing specific natural antibodies and complement. Blood 2002; 99:2477–2482
6 Cheng Y, Cheng G, Chui CH, et al.: ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 2005; 293:1450–1451
7 Zhao J, Yang Y, Huang H, et al.: Relationship between the ABO blood group and the COVID-19 susceptibility. Clin Infect Dis 2020. Available online: https://doi.org/10.1093/cid/ciaa1150.
8 Zietz M, Tatonetti NP: Testing the association between blood type and COVID-19 infection, intubation, and death. medRxiv preprint. Available online: https://doi.org/10.1101/2020.04.15.20058073.
9 Zeng X, Fan H, Lu D, et al.: Association between ABO blood groups and clinical outcome of coronavirus disease 2019: Evidence from two cohorts. medRxiv preprint. Available online: https://doi.org/10.1101/2020.04.15.20063107.
10 Li J, Wang X, Chen J, et al.: Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol 2020; 190:24–39. https://doi.org/10.1111/bjh.16797.
11 23andMe finds evidence that blood type plays a role in COVID-19. Available online: https://blog.23andme.com/23andme-research/23andme-finds-evidence-that-blood-type-plays-a-role-in-covid-19/ [accessed on 20 August 2020].
12 Ellinghaus D, Degenhardt F, Bujanda L, et al.: The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. N Engl J Med. 2020, Jun 17:NEJMoa2020283. [Epub ahead of print].
13 Yamamoto F: ABO blood groups and SARS-CoV-2 infection. ResearchGate. Available online: https://doi.org/10.13140/RG.2.2.30970.72648.
14 Gérard C, Maggipinto G, Minon J-M: COVID-19 & ABO blood group: another viewpoint. Br J Haematol 2020; 190:e93–e94. https://doi.org/10.1111/bjh.168847.
15 Tregouet DA, Heath S, Saut N, et al.: Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood 2009; 113:5298–5303
16 Latz CA, DeCarlo C, Boitano L, et al.: Blood type and outcomes in patients with COVID-19. Ann Hematol 2020; 99:2113–2118
17 Dzik S, Eliason K, Morris EB, et al.: COVID-19 and ABO blood groups. Transfusion 2020; 60:1883–1884. Available online: https://doi.org/10.1111/trf.15946.