

Editorial

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Unraveling the mystery of blood groups and COVID-19

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Prior to the discovery of ABO blood group antigens, the outcome of blood transfusion was unpredictable, with some patients appearing to benefit from transfusion while others experienced severe complications that resulted in death [1]. The discovery of ABO blood group antigens on the surface of red blood cells (RBCs) and corresponding anti-A and anti-B antibodies not only provided the first example of polymorphism in the human population, but also suggested a possible cause of the disparate outcomes that could occur following transfusion. As anti-A and anti-B antibodies form spontaneously without known prior exposure events, virtually all patients that do not express the A or B antigen generate varying levels of anti-A and anti-B antibodies. As a result, prior to transfusion and transplantation, ABO blood group expression and anti-A and anti-B antibodies are tested to ensure compatibility and therefore reduce the chance of life-threatening immunological reactions [2, 3].

Following the discovery of ABO blood group antigens, subsequent studies demonstrated that RBC polymorphisms are not limited to ABO blood groups, but that additional polymorphisms can exist on RBCs, including RhD. Unlike alloantibodies that form against the A and B blood groups, alloantibodies against RhD and nearly 300 other alloantigens do not typically form spontaneously, but instead emerge following exposure to RBCs as a result of pregnancy or blood transfusion. Given the immunogenicity of RhD and its prominent role in the etiology of hemolytic disease of the fetus and newborn (HDFN), ABO and RhD antigens are examined prior to blood transfusion to not only avoid hemolytic transfusion reactions, but also reduce the probability that transfusion induces anti-RhD alloantibodies that could complicate future transfusions and mediate HDFN.

A simple screen test is also employed to determine whether a patient has developed alloantibodies against other RBC alloantigens. We now understand that alloantibody development is not limited to blood group antigens, but of course can be a major barrier to transplantation and the delivery and efficacy of other therapeutic interventions [4, 5].

As ABO and RhD testing is conducted prior to transfusion, transplantation, and at the onset of pregnancy, ABO and RhD blood group antigens are the most frequently analyzed polymorphisms in the human population. With blood group antigen data readily available, ever since the implementation blood group testing in clinical practice, there has been a longstanding inclination to correlate these polymorphisms with diverse disease conditions. Blood donors, who likewise undergo blood group antigen testing to ensure compatibility with potential recipients, often serve as the healthy control population in these studies. As additional blood group antigens were described, the use of blood group antigens became a major focal point in seeking to define possible genetic determinants of various diseases. Indeed, such an approach inadvertently resulted in the discovery of the Australia antigen, later shown to not be a blood group, but instead a viral antigen associated with hepatitis B (the hepatitis B surface antigen) [6]. Such efforts illustrate the many attempts to harness the insight blood group antigens when seeking to discern the genetic underpinnings of different diseases.

While these attempts are to be lauded, particularly considering the limited tools available to ascertain genetic variances among individuals, they suffered from many of the biases that persist today when seeking to establish associations between blood group status and disease. As blood donor centers prefer blood group O donors given the “universal” compatibility of blood group O RBCs, these centers understandably emphasize recruitment of blood group O individuals, often leading to a higher representation of blood group O healthy donors relative to their prevalence in the wider population. Consequently, it is not surprising that numerous early studies — though not all — suggested that individuals with blood group O may be partially protected for a given disease state when compared to blood group A individuals. Such biases have been reduced by focusing on

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first-time blood donors, as their blood group distribution is anticipated to more closely mirror the broader population.

Despite limitations in prior studies, prospective approaches designed to avoid these potential confounders have continued to find correlations between disease predispositions and ABO blood group antigens [7]. This has been most notable in cardiovascular disease and infection. The association between blood group A expression and higher levels of von Willebrand factor (vWF), which is correlated with an elevation in thromboembolic cardiovascular complications, provides the most compelling explanation for why individuals who are blood group A may be more likely to experience thromboembolic and related cardiovascular complications. Indeed, vWF levels are the only value routinely tested for clinically where established reference ranges are predicated on ABO blood group status. ABO blood groups have also been shown to influence some types of infection, including cholerae and malaria. Such correlations probably stem from the specific influence of ABO blood group expression on pathogen engagement or the ramifications of microbial toxins on host cells.

The COVID-19 pandemic provides the latest example of the potential linkage between ABO blood group status and disease susceptibility. Intriguingly, the associations with COVID-19 not only pertain to infection susceptibility but also extend to disease severity, which can be driven in part by thromboembolic complications. As a result, the associations between COVID-19 and ABO blood group antigens appear to intertwine the two most common correlations previously observed. In this issue of the *Journal*, Franchini and colleagues provide an excellent overview of the numerous studies that have been conducted on COVID-19 and ABO blood groups, spanning epidemiological findings to mechanistic insight into how ABO(H) antigens may influence COVID-19 outcomes [8]. In doing so, the accompanying review highlights the distinct nature of the studies that have been conducted. While some studies suffer from the same potential biases that have existed since the discovery of ABO blood group antigens, others employed a remarkably objective approach and continued to find similar associations between ABO blood groups and COVID-19. Given the various tissue expression patterns of ABO antigens, this review also outlines different hypotheses and accompanying data that provide possible mechanistic insight. These data include the possibility that ABO blood group antigens may be directly engaged by the SARS-CoV-2 receptor binding domain

to influence SARS-CoV-2 attachment to respiratory epithelial cells and the ability of anti-ABO(H) antibody to engage A or B antigens incorporated into the virus itself and therefore possibly prevent infection [9, 10]. The associations of ABO blood groups with vWF and disease severity is also examined.

Taken together, this review provides a succinct overview of the various ways blood group antigens can impact basic biology and COVID-19. In doing so, the review provides important insight into the ongoing evolution of blood group antigens and a snapshot of the evolutionary pressures that may have shaped their selection during human evolution. Regardless of why ABO polymorphisms persist in the human population, given their continual assessment in transfusion, transplantation and maternal-fetal medicine, associations between the earliest polymorphisms described in the human population and new disease entities are sure to continue.

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