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More on 'Association between ABO blood groups and risk of SARS-CoV-2 pneumonia'

We read with interest the recent report from Li *et al.*[1] describing an association between ABO blood groups and risk of SARS-CoV-2 pneumonia. In an initial study of 265 patients with COVID, the authors observed that blood group O individuals were significantly underrepresented amongst patients who required hospitalization for severe COVID-19 infection ($P < 0{\cdot}01$). Conversely, blood group A was significantly more common in patients with severe COVID-19 compared to the local population ($P = 0{\cdot}017$). Subsequently, in a larger validation cohort that included 2 153 patients with COVID-19, this ABO effect was reproduced with blood group O again being associated with a significant protective effect ($P < 0{\cdot}001$). In keeping with these data, another independent study ($n = 2\ 173$) also reported that blood group O was associated with reduced susceptibility to severe COVID-19.[2] Since the pathogenesis underlying COVID-19 remains poorly understood, we believe that these novel findings provide interesting insights into biological mechanisms that may contribute to interindividual differences in COVID-19 susceptibility.

The importance of ABO blood group in blood transfusion and clinical transplantation is well established. In addition, multiple studies have shown that ABO blood group is an important independent risk factor for cardiovascular disease and venous thromboembolism (VTE).[3,4] In particular, risk of thrombosis is significantly reduced in blood group O compared to non-O individuals. More recent data have defined biological mechanisms through which ABO modulates thrombotic risk.[5–7] Given the accumulating evidence demonstrating that COVID-19 is associated with a significant coagulopathy[8,9] and that microthrombi disseminated through the lung vasculature contribute to acute respiratory distress syndrome (ARDS),[10,11] the association between ABO blood group and COVID-19 susceptibility is of particular interest.

Although ABO(H) blood group carbohydrate structures are traditionally considered red blood cell antigens, they are actually expressed on a range of other cell types, including endothelial cells (EC) and platelets.[12] In addition, covalently-linked ABO(H) determinants are also present on a number of plasma glycoproteins, including von Willebrand factor (VWF), and factor VIII (FVIII).[13] Importantly, the ABO(H) sugars on VWF have been shown to influence its biological activity. First, plasma VWF levels are 20–30% lower in normal blood group O individuals compared to non-O subjects.[5] These reduced VWF levels are due to the fact that group O VWF has a significantly reduced plasma half-life compared to non-O VWF (10·0 compared to 25·5 h).[14] Since FVIII circulates in high-affinity complex with VWF, plasma FVIII:C levels are also significantly reduced in blood group

O individuals. Second, ABO(H) blood group determinants on VWF have also been shown to regulate susceptibility to proteolysis by ADAMTS13. In particular, group O VWF is cleaved significantly more rapidly by ADAMTS13 compared to non-O VWF.[6] Finally, ABO sugars on both VWF and platelet GPIb have been demonstrated to influence VWF-dependent platelet aggregation under shear stress.[7,15] Cumulatively, these ABO effects on VWF/FVIII and platelet biology undoubtedly play a major role in determining the reduced risk of thrombosis observed in blood group O subjects.

With respect to the relationship between ABO blood group influencing COVID-19 susceptibility, it is important to note that markedly elevated plasma VWF:Ag and FVIII:C levels have been reported in patients with severe COVID-19 pneumonia.[16] Since VWF and FVIII are both synthesized predominantly within EC, these data support the hypothesis that severe COVID-19 infection is associated with marked EC activation and Weibel Palade body exocytosis. Interestingly, the ACE-2 receptor utilized by COVID-19 to gain cellular entry is expressed on EC.[17] In addition, ABO(H) blood group antigens are also expressed on EC surfaces. Further studies will be required to determine the relative importance of plasma VWF/FVIII levels and EC activation in the pathogenesis underlying COVID-induced coagulopathy and pulmonary microvascular occlusion. Nevertheless, it is striking that acute EC activation and secretion of pathological ultra-large VWF multimers have previously been implicated in contributing to cerebral microvascular occlusion in children with severe *Plasmodium falciparum*.[18,19] Similar to COVID-19, blood group O individuals are significantly less susceptible to developing cerebral malaria,[20] the pathological hallmark of which is microvascular occlusion.

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