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Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19?

The *British Journal of Haematology* recently published two papers describing autoimmune haemolytic anaemia (AIHA) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1,2] AIHA is characterised by the destruction of red cells by autoantibodies, but the mechanism underpinning autoimmunity in patients with coronavirus disease 2019 (COVID-19) has yet to be elucidated.

We recently postulated that molecular mimicry could be at the basis of the most severe complications observed in SARS-CoV-2-induced disease (COVID-19).[3,4] For example, antibodies elicited against viral proteins could very well cross-react with vascular endothelial proteins if they shared antigenic epitopes. This would trigger extensive vasculitis followed by thrombosis and widespread intravascular coagulation with multi-organ failure.[5]

Here, we would like to posit the hypothesis that molecular mimicry is also a determinant factor in AIHA in patients with COVID-19, with Ankyrin 1 (ANK-1) and the viral protein Spike being the central players.

ANK-1 is an erythrocyte membrane protein that is important for red cell differentiation and function, providing the primary connection between the membrane skeleton and the plasma membrane.[6] It is defective in patients with hereditary spherocytosis, a common cause of haemolytic anaemia.[6]

We found that ANK-1 shares a putative immunogenic-antigenic epitope (amino acids LLLQY) with 100% identity with the SARS-CoV-2 surface glycoprotein named Spike protein (Table I). We established that this epitope is part of the Spike's predicted immunogenic epitope 750-SN**LLLQY**GSFCTQL-763 for B cells by using the immune epitope database and analysis resource [Immune Epitope Database (IEDB), https://www.iedb.org/]. This database contains experimentally validated epitopes and tools to predict epitopes recognisable be T and B cells and is used also in the design of vaccines.[7]

With this Letter, we would like to call the attention of the scientific community to the structural similarity between ANK-1 and the viral protein Spike. We hope it will prompt further research aiming at determining if the potential immunological cross-reactivity between ANK-1 and Spike contributes to the pathogenesis of AIHA in patients with COVID-19. Information on this topic may open new avenues toward designing efficacious therapies.

Table I. Shared identical epitope between Ankyrin 1 and SARS-CoV-2 surface glycoprotein[1]

Protein	Accession number	Epitope amino acids	Identity percentage, %
SARS-CoV-2 surface glycoprotein	NCBI ID: YP_009724390·1	752-LLLQY-756	100
Ankyrin 1	UniProt ID: P16157	323-LLLQY-327	

ID, identifier; NCBI, National Center for Biotechnology Information.
[1]We used for comparative analyses BlastP (available at: https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins) and the whole virus proteome (available at: https://www.ncbi.nlm.nih.gov/nuccore/MN908947).

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COVID-19 and ABO blood group: another viewpoint

Li *et al.*[1] have recently published '*Association between ABO blood groups and risk of SARS-CoV-2 pneumonia*', an observation already reported a few weeks ago as a MedRxiv preprint by Zhao *et al.*[2] and which had a certain impact in the press.

In both studies, the ABO blood groups distribution of patients with coronavirus disease 2019 (COVID-19) were compared to that of controls from the local populations that showed that blood group A was associated with an increased risk of infection, whereas group O was associated with a decreased risk. Considering this information rather as a working hypothesis, some scientists have called for caution.[3]

However, as already strongly suggested by others,[4] this variable susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could be linked to circulating anti-A antibodies, which could interfere or even inhibit the virus–cell adhesion process.

We had the idea to analyse these important available data series from the anti-A or -B antibodies viewpoint instead of ABO blood group antigens as the authors did.

In fact, considering the largest series of patients with COVID-19 ($N = 1888$) analysed by Zhao *et al.*,[2] we compared the proportion of those possessing anti-A in their serum (i.e. those of B and O blood groups) and those who