How blood group A might be a risk and blood group O be protected from Coronavirus (COVID-19) infections

by Peter Arend

When according to the numbers of Wikipedia (although they might be disputed) in countries like Chile, Ecuador, Colombia, Simbabwe and Mexico 59 to 85 percent of the people have blood group O and these countries officially publish extremely low COVID-19 cases and death rates per 1 million inhabitants, this might suggest a lower susceptibility of blood group O to the disease, although this blood group can no longer be considered a genetic entity.[1] Unusual O alleles including O2 have been described at the ABO locus, which implicates unexpected phenotypes, involving weak blood group A alleles.

The molecular biology of a virus infection pathogenesis determines the genetic target and the human phenotype-determining enzymes decide about the fundamental difference between infection and disease. In the case that *O*-glycosylation plays a key role in the pathogenesis of coronavirus disease, as was discussed already 14 years ago in a SARS-CoV infection[2] and is currently again predicted for SARS-CoV-2 or COVID-19,[3] this would involve the formation of hybrid, serologically A-like, *O*-GalNAcα1-Ser/Thr-R, Tn ("T nouvelle") antigenic structures. The virus cannot survive outside of its hosts and hypothetically utilizes the host cell's machinery via hijacking its A-like/Tn formation by serine-rich motifs. Similar suggestions are subject of the recent review, published by Watanabe et al. (2019).[4]

The adhesion of the virus to host cells would primarily occur independent of the ABO blood group through the genetically undefined intermediate, A-like/Tn evolutionary/developmental structure, which is common to all metazoan growth processes and apparently acts as a

host-pathogen functional bridge in different, unrelated infectious diseases.[5, 6] However, apart from the fact that susceptibility to an infection and its severity depend on many factors, individuals with blood group A could not respond with either acquired or innate antibodies to the synthesis of hybrid A-like structures due to clonal selection and phenotypic, glyosidic accommodation of plasma proteins:[7] The ABO(H) blood group phenotype formation occurs on both the cell surfaces and plasma proteins, and while in the human blood group O(H) the polyreactive nonimmune or innate immunoglobulin M (IgM) controls the expression and qualities of the syngeneic A-like/Tn structures, the anti-A, B and H-isoagglutinin activities (exerted by the neonatal IgM molecule) are neutralized through the ABH-phenotype-determining enzymes in the non-O blood groups. Thus, blood group A individuals must become a preferred target for the virus, which hypothetically mimicks the ABO phenotype pathways.

Serine residues, preserved on the viral spike protein, become available through the action of the host's transmembrane serine protease TMPRSS2,[8] while the ACE (angiotensin converting enzyme) receptor protein, apparently codetermined by the ABO phenotype,[9, 10, 11] might provide the ABO glycan transferring enzyme activity, which performs a further (blood group-A-specific mucin-type) hybrid binding. Analogously, the binding to blood group O cells occurs by mucin-type fucosylation via fucosyltranferases 1 and 2 (FUT1/FUT2) activities and performance of a hybrid H-type antigen,[5, 6] which does not affect the innate and adaptive anti-A isoagglutinin levels (Fig. 1). Again, within the complex molecular pathogenic process, the most critical molecular step appears to be the mobilization of the viral serine molecule, provided by the host’s TMPRSS2 protease,[8] while the virus penetrates the cell wall and/or enters the cell via an intermediate

functional, blood group-specific *O*-glycan in a process, which yet remains unclear in detail.

Interactions between different pathogenic viruses and human ABO(H) glycans are known for decades and are explained by similar molecular biological models. A human rotavirus interacts with A-type histo-blood group antigen and its infectivity was specifically abrogated by anti-A antibodies.[12] Appropriately, the analysis of a SARS-CoV outbreak in Hongkong 2008 revealed that blood group O was associated with low risk of infection,[13] while *in vitro* studies showed that the interaction between the viral spike protein and the host's cellular receptor was inhibited by natural and monoclonal anti-A antibodies. Finally, the actual and first statistical study indicates that people with blood group A have a significantly higher risk for acquiring SARS-CoV-2 or COVID-19 infection, whereas people with blood group O have a significantly lower risk for the infection compared with non-O blood groups.[14] While this observation awaits confirmations, blood group O individuals, lacking the blood group-A-determining enzyme, may develop the least molecular contact with the pathogen and maintain the anti-A/Tn cross-reactive, complement-dependent isoagglutinin activities, which are exerted by the polyreactive, nonimmune immunoglobulin M (IgM),[5, 6, 15] representing the humoral spearhead of innate immunity and a first line of defense.

References:

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Proposed (virtual) adhesion and/or response

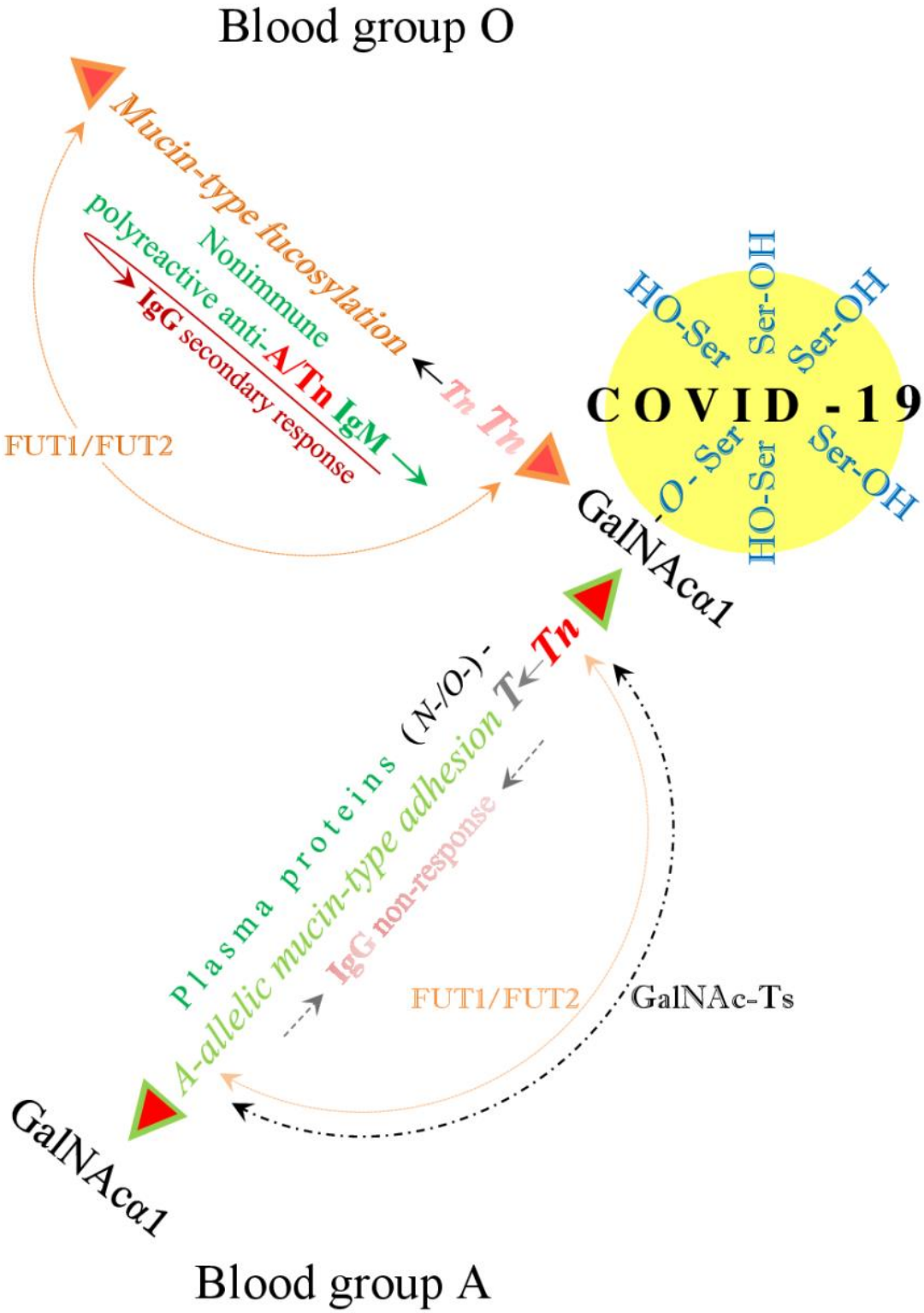

Figure 1. The virus cannot survive outside of its hosts and hypothetically mimicking the ABO phenotype synthetic pathways, utilizes the host cell's machinery via hijacking the host's A-like/Tn formation and phenotype-determining enzymes by serine-rich motifs. The ABO(H) phenotype formation occurs on the both cell surfaces and plasma-proteins:[7] while in blood group A the naturally-occurring anti-A and anti-H antibody activities, exerted by the polyreactive, nonimmune IgM molecule, are neutralized by the phenotype-determining glycotransferases (FUT1/FUT2 and GalNAc-Ts), in blood group O the anti-A activites remain unaffected. This figure was constructed according to figure 2 in a previous article, in which this mechanism may be similarly utilized by a non-viral pathogen, such as the protozoan parasite *Plasmodium falciparum* (See references 5 and 6).