How blood group A might be a risk and blood group O be protected from SARS-CoV-2 (COVID-19) infections (how the virus invades the human body via ABO(H) blood group-determining carbohydrates).

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Abstract.

While the angiotensin converting enzyme 2 (ACE2) is defined as the primary SARS-CoV-2 (Severe acute respiratory syndrome-related coronavirus 2) receptor, the serine molecule, which is mobilized by the host's TMPRSS2 (transmembrane protease serine subtype 2) from the viral (S) spike protein, hijacks the N-acetyl-D-galactosamine (GalNAc) metabolism of the host, and the resulting hybrid, serologically A-like/Tn (T-nouvelle) structure causes the virus to adhere to the host's cells. In humans, this intermediate structure will hypothetically be replaced by ABO(H) blood group-specific, mucin-type, in the case of infection hybrid epitopes, implicating the phenotypically glycosidic accommodation of plasma proteins. The virus may, mimicking the synthetic pathways of the ABO(H) blood groups, bind to the cell surfaces of the blood group O(H) by formation of a hybrid H-type antigen or hybrid precursor of the non-O blood groups, which does not affect the highly anti-glycan aggressive anti-A and anti-B isoagglutinin activities, exerted by the germline-encoded nonimmune immunoglobulin M (IgM). In the non-O blood groups, which have developed from the H-type-antigen, these activities are downregulated by phenotypic glycosylation, while adaptive immunoglobulins might arise in response against the hybrid A and B blood group structures, which suggesting to exert autoreactivity. The non-O blood groups thus become a preferred target for the virus, whereas blood group O(H) individuals, lacking the A/B phenotype-determining enzymes and binding the virus alone by hybrid H-type antigen formation, have the least molecular contact to the virus and maintain the critical anti-A and anti-B isoagglutinin activities, exerted by the ancestral IgM, which is considered the humoral spearhead of innate immunity.

Keywords: COVID-19; SARS-CoV-2- human carbohydrate interaction, trans-species glycosylation; A-like/Tn formation, glycan trans-species bridge.

Introduction.

Infection does not mean disease because the invasion of a pathogen does not always lead to symptoms. Apart from innumerable other factors, this phenomenon mainly results from the different qualities and degrees of the physical and chemical bonding types between host and pathogen and reflects the actions of the host's phenotype-determining enzymes. The molecular biology of an infection pathogenesis determines the susceptibility of a species to the infection, while the development of symptoms or the severity of the subsequent disease depend on the phenotype. In the case that *O*-glycosylation plays a key role in the pathogenesis of coronavirus diseases, as was discussed already 14 years ago in SARS-CoV-1 infection (Oostra *et al.*, 2006) and is currently again predicted for SARS-CoV-2 or COVID-19 (Andersen *et al.*, 2020), this would implicate the formation of hybrid, serologically A-like, *O*-GalNAcα1-Ser/Thr-R, Tn antigenic structures (Arend, 2020a). This prediction may not be not consistent with the concept of (Guillon *et al.*, 2008), according to which viruses bind to hosts by *N*-glycosylations when in their study on SARS-CoV-1 infection the interaction between the viral spike protein and the host's cellular receptor was inhibited by natural and monoclonal anti-A antibodies. However, the history of the amino acid serine molecule will show that the host's *O*-glycoproteome plays the key role in SARS-CoV-2 infection pathogenesis. The adhesion of the virus to host cells primarily appears to occur independently of the ABO(H) blood group through the genetically undefined intermediate, serologically A-like/Tn evolutionary/developmental structure, which is common to all metazoan growth and/or ontogenetic processes, and which through its hybridized form apparently acts as a host–pathogen functional bridge in different,

unrelated infectious diseases (Arend, 2018b; 2020b). In fact, when the angiotensin-converting-enzyme 2 (ACE2) protein is defined as the primary SARS-CoV-2 receptor, the following data strongly account for an actual binding between host and pathogen via an intermediate hybrid *O*-glycan, dominated by the pathogen's hydrophilic amino acid serine. In the human species this ontogenetic, blood group independent structure may, depending on the phenotype, be elongated and/or replaced by mucin-type blood group-specific, ABO(H) phenotype-determining carbohydrates according to established pathways (Vitiazeva *et al.*, 2015).

How blood group A might be a risk and blood group O be protected from SARS-CoV-2 (COVID-19) infection.

The coevolution of species drives diversity in animals and plants and contributes to natural selection, while during an infectious disease, a pathogen may complete an incomplete evolutionary/developmental function by utilizing the host cell's machinery (Arend, 2020b). Analysis of related older data suggests that *Plasmodium falciparum* (*P. falciparum*), the pathogen of malaria tropica, cannot survive outside its human host because it is unable to perform the evolutionarily first protein glycosylation or blood group-independent (serologically A-like) *O*-GalNAcα1-Ser/Thr-R, Tn antigen formation owing to its inability for synthesizing the amino sugar N-acetyl-D-galactosamine (GalNAc) (Dieckmann-Schuppert and Bause, 1993) nor does it possess genes required for mucin-type *O*-glycan synthesis (Templeton *et al.*, 2004).

Although a non-viral pathogenesis cannot be compared to a viral pathogenesis, the following data strongly suggest an invasion of SARS-CoV 2 into the human cell by the formation of an

intermediate hybrid *O*-glycan. The virus cannot survive outside of its hosts, and hypothetically utilizes the host cell's machinery via hijacking its A-like/Tn formation by liberation of serine molecules. Similar suggestions have been the subject of the recent review, published by Watanabe, Y. *et al.* (2019). The virus enters the human body through the human ACE2 protein, which is a polyfunctional protein and, among various other functions, represents the binding domain of the SARS-CoV viruses. In a complex signaling pathway the human ACE2 binds to the spike (S) protein of the virus envelope (Inoue *et al.*, 2007) and after subsequent cleavage of the ACE-virus S-protein complex by cathepsin L (Simmons *et al.*, 2005)**,** the virus enters the cell by receptor-mediated endocytosis (Wang *et al.*, 2008). Within the ongoing discussion, as to which amino acids dominate the host–pathogen fusion, the most critical molecular step appears to be the mobilization of the viral serine molecule, performed by the host's TMPRSS2 protease (Matsuyama *et al.*, 2010; Hoffmann *et al.*, 2020).

The history of this hydrophilic amino acid and its obviously essential involvement in SARS-CoV-2 pathogenesis strongly suggest that the binding between pathogen and host occurs by *O*-glycosylation. Although serine-rich repeat proteins (SRRPs) performing the adhesion of different bacteria (Latousakis *et al.*, 2020) and other microrganisms, such as a malaria parasite (Bzik *et al.*, 1988) or an entamoeba (Zhang *et al.*, 1994) to host cell carbohydrates via *O*-glycosylation, and a dominance of the *O*-glycoproteome were not yet described for a virus infection pathogenesis, such a mechanism might take place in SARS-CoV pathogeneses. In view of this concept, the observation that the adhesion of the SARS-CoV-2 spike protein to its cellular receptor was

inhibited by monoclonal and natural anti-histo-blood A group antibodies (Guillon *et al.*, 2008) might have evidenced the presence of the classical *O*-GalNAc binding to a serine molecule. Finally, the preferential occurrence of a severe disease in individuals with non-O blood groups demonstrates that the blood group A and B phenotype-determining sugars are the crucial *O*-glycosidic target. Serine residues, preserved on the viral spike protein, may become available through the action of the host's TMPRSS2 protease (Hoffmann *et al.*, 2020), while the ACE2 receptor protein, hypothetically codetermined by the ABO(H) phenotype (Cidl *et al.*, 1996; Gassó *et al.*, 2014; Terao *et al.*, 2013), mediates the ABO(H) glycan transferring enzyme activity, performing a further (blood group-A and/or B-specific mucin-type) hybrid binding. Analogously, the final binding to blood group O(H) cells might occur by mucin-type fucosylation via fucosyltranferases 1 and 2 (FUT1/FUT2) activities and performance of a hybrid H-type antigen involving the physiological loss of innate anti-H (Arend, 2018b; 2020b), which does not affect the innate and adaptive anti-A and and anti-B isoagglutinin levels (Figures 1and 2). Again, within the complex molecular pathogenic process, the most critical molecular step appears to be the mobilization of the viral serine molecule (Hoffmann *et al.*, 2020), which accesses both the host's blood-group independent (ontogenetic) and blood group-specific (A-allelic-encoded) *O*-GalNAcα1-Ser/Thr-R (Tn) formations, whose evolutionary relationship remains unknown. This means, that although the ACE2 protein is defined as the SARS-CoV-2 virus receptor and mediates the transferring enzyme activities, the actual and/or additional binding between host and pathogen appears to be an intermediate hybrid *O*-glycan.

ABO(H) blood group phenotype formation dominates innate immune.

Humoral innate immunity or the first line of defense and its complex connection with ABO(H) phenotype formation are considered to play the main role in SARS-CoV-2 infection and severity of the subsequent disease. In contrast to adaptive, environmentally-induced immunoglobulin or B-cell activities, which are controlled by clonal selection, the production of the innate, nonimmune and polyreactive immunoglobulin M (IgM) is not restricted to B cells but spontaneously occurs in murine (Zhou, O'Hara and Chen, 2011; Shao *et al.*, 2016) and human (F. Hu *et al.*, 2012) normal and malignant epithelial cells as well. An early ovariectomy of an inbred mouse (Arend and Nijssen, 1976; 1977; 1977a) revealed that in the mammalian species this IgM molecule is structurally connected with the ancestral A-like/Tn antigen through a complex evolutionary process (Arend, 2016), and it is considered its complementary protein. Hammarström (1973) showed that ancestral glycans arising during germ cell maturation from *O*-glycosylations by lower metazoans, such as the snail *Helix pomatia*, are associated with the release of a hexamerically structured anti-A/Tn-complementary hemagglutinating defense protein. Intriguingly, the binding patterns and the capacity of this molluscan protein to bind human blood group A RBCs are strikingly similar to those of the mammalian IgM molecule, giving rise to speculation regarding an evolutionary relationship with the mammalian nonimmune anti-A-reactive IgM molecule (Arend, 2018b). In fact, the production of this molecule cannot not be stimulated by environmental A-like antigens; its levels remain unaffected after immunization with microbial A-reactive lipopolysaccharides, and

the innate IgM can simply be separated from the adaptive IgM by absorption (Arend, 1971). In humans, the innate IgM molecule is subject to the phenotypic accommodation of plasma proteins, wherein it is enzymatically tailored to the ABO(H) blood group isoagglutinin specificities. Protein glycosylation is thought to occur intracellularly in the Golgi cisternae. Accordingly, during immunoglobulin secretion, the poorly glycosylated intracellular IgM molecule becomes loaded with L-fucose and D-galactose (Andersson and Melchers, 1973), which subsequently expressed by the extracellular IgM, might form the basis of phenotypic accommodations. Hypothetically, soluble plasma glycotransferases are involved in this process: blood platelets for example, have been detected as a rich source of both glycosyltransferases and energy-rich sugars and amino sugars that are released from activated platelets to function in the extracellular space (Wandall *et al.*, 2012; Lee-Sundlov *et al.*, 2017).

Ultimately, innate immunity develops in evolutionary and molecular connection with ABO(H) blood group phenotype formation, involving both the cell surfaces and plasma proteins in identical glycosylations, which in normal conditions physiologically precludes a corresponding natural autoreactivity, exerted by the ancestral nonimmune or neonatal IgM (Arend, 2016). In the case of infections, such as SARS-CoV-2, this principle enables the formation of foreign hybrid structures. While in the human blood group O(H) the nonimmune IgM molecule exerts the highly anti-glycan-aggressive activities, involving an adaptive response by immunoglobulin G (IgG) antibodies and attacking any non-complementary, hybrid structure formations, in the non-O blood groups corresponding anti-A and B-isoagglutinin activities are phenotypically neutralized through the blood group A

and B phenotype-determining glycotransferases, and a secondary IgG response is precluded due to clonal selection (Arend, 2018b; Arend, 2017). Therefore, the non-O blood group individuals become a preferred target for SARS-CoV-2, which somehow mimics the ABO(H) phenotype synthetic pathways.

SARS-CoV-2 infections occur independently of the ABO(H) blood group via the intermediate A-like/Tn adhesion principally in all metazoan but the development and severity of the human disease, which in principle may be an autoimmune disease, appears mainly, apart from uncountable other factors, to be determined by the ABO(H) phenotype. The physiological lack of innate anti-A and anti-B antibodies in the non-O blood groups A, B and AB poses the immunological dilemma in these blood groups: on one side, it protects them from self-reactivity against complementary structures, but on the other side, it cannot prevent the formation of hybrid, most likely autoantigenic targets, arising in a subsequent pathogenic step. It is assumed, that in SARS-CoV-2 infection, especially in the non-O blood groups the induction of autoimmune processes might contribute to the development of severe disease, which may even be dominated by autoimmune inflammations. Such a phenomenon was also suggested in severe malaria tropica disease (Hart *et al.*, 2016; Rivera-Correa *et al.*, 2017) and was explained by the author via hybridization (Arend, 2020b). The proposed relationships between the degree of phenotype diversity and the presence of humoral innate and adaptive responses is illustrated in Figure 1; phenotype-depending response and proposed autoimmune response are demonstrated in Figure 2.

Syngeneic and SARS-CoV-2 hybrid ABO(H) mucin-type formation
Nonimmune humoral "corresponding" response

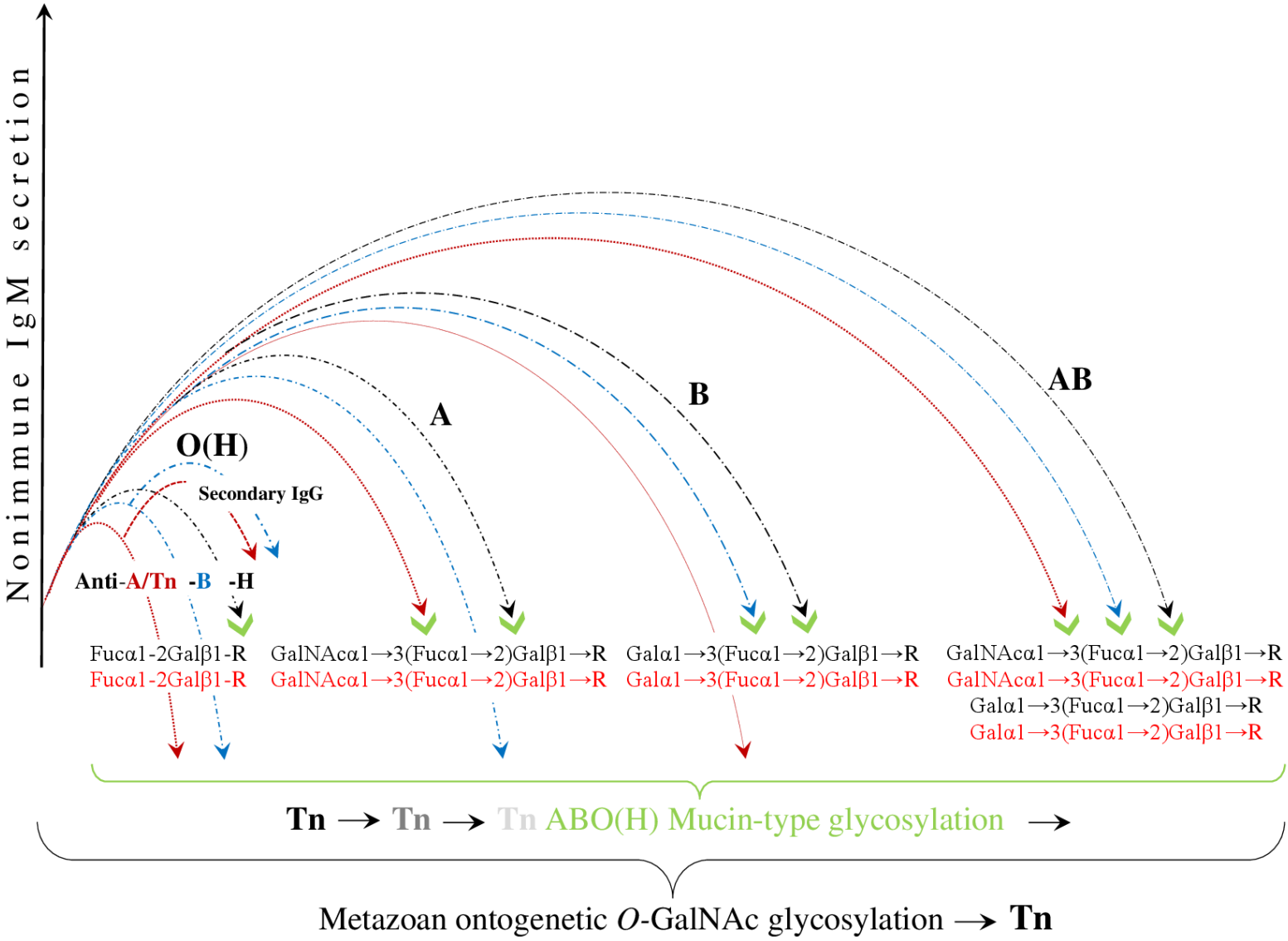

Figure 1

Figure 1.

The virus, mimicking the synthetic pathways of the ABO(H) blood groups, binds to the cell surface of the blood group O(H) by formation of a hybrid H-type antigen or hybrid precursor of the non-O blood groups, which does not affect the highly anti-glycan aggressive anti-A and anti-B isoagglutinin activities, exerted by the germline-encoded nonimmune immunoglobulin M (IgM). In the non-O blood groups, developing from the H-type-antigen, these activities are downregulated by phenotypic glycosylation, while the hybrid A- and B-type structures to an unknown extent will exert autoreactivity. The infection is initiated via trans-species blood group-independent, metazoan ontogenetic GalNAc glycosylation or A-like/Tn formation, which in the human is prolonged or replaced by mucin-type ABO(H) blood group-specific formation. Augmenting phenotype diversity is hypothetically associated with decreasing innate immunity: blood group O(H) solely neutralizes the anti-H activity, exerted by the nonimmune IgM but maintains the critical anti-A and an anti-B isoagglutinin activities; it develops the least contact with the pathogen and shows the strongest response. The blood groups A and B maintain the non-corresponding anti-A and anti-B isoagglutinin activities respectively, however, they do not produce a secondary IgG and cannot prevent the formations of foreign antigenic, hybrid structures. Blood group AB develops the strongest contact with the pathogen and shows no "corresponding" response due to phenotypic accommodation of plasma proteins and clonal selection. The immunoglobulin classes and levels of adaptive, "non-corresponding" antibodies, most likely arising against the hybrid structures are unknown and are ignored in this figure.

Conclusions.

The proposed concept of a virus invasion initiated by mobilization of the serine molecule from the viral spike protein and completed by formation of a hybrid, genetically undefined A-like/Tn trans-species molecular bridge, does not question the established functions of the ACE2 receptor protein in its previous (Wu *et al.*, 2011) and current definitions (Zhou *et al.*, 2020; Armijos-Jaramillo *et al.*, 2020) but rather shows an additional and more specific interaction between host and pathogen. Both *N*- and *O*-glycosylations may occur within this complex pathogenic process, and among multiple chemical and physicochemical linkage options, both a trans-species ontogenetic or blood group-independent and blood-group specific binding may be performed through *O*-glycosylations in two different glycosidic steps, dominated by the pathogen's hydrophilic amino acid serine; moreover, a blood group-specific, mucin-type formation appears to elongate and/or replace the trans-species, ontogenetic binding. The prominent evolutionary position of the serine molecule has again been revealed for SARS-CoV-2 infection, and is evident also in other, unrelated infectious diseases, such as malaria tropica, due to the discovery of the serine repeat antigen SERA in malaria tropica (Arend, 2018b; Bzik *et al.*, 1988; Aoki *et al.*, 2002; Arisue *et al.*, 2011) or *Entamoeba histolytica* infection, in which the serine-rich *E. histolytica* protein STREHP (ZHANG *et al.*, 1994; Stanley *et al.*, 1995) dictates the binding and virulence of the parasite (Manochitra K, 2017). It is proposed that Covid-19 infection is initiated by intermediate hybrid A-like/Tn antigen formation, hijacking the physiological, genetically undefined, serologically A-like/Tn ontogenetic structure, which must be differentiated from the human blood group A-specific epitope (Figure 2). This is encoded by the A allele of the ABO gene located on chromosome 9q34, which together with the B-

allele determines the risk of developing life-threatening disease in the non-O blood groups (Arend, 2020b). Interactions between different pathogenic viruses and human ABO(H) glycans have been known for decades, and can be 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 (L. Hu *et al.*, 2012). Appropriately, the comprehensive study by Guillon *et al.* (2008) as cited above, and their analysis of a SARS-CoV-1 outbreak in Hongkong in 2003 revealed that blood group O(H) was associated with low risk of infection, while the interaction between the viral spike protein and the host's cellular receptor was inhibited by natural and monoclonal anti-A antibodies in vitro. Finally, the actual and first statistical study indicated 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 (Zhao *et al.*, 2020). While this observation awaits confirmation, the central immunological position of the human blood group O(H) might have already become evident in a small study 50 years ago (Arend and Fehlhaber, 1969), which has been widely discussed in recent works (Arend, 2017; 2018b; 2018a), Figure 3.

SARS-Cov-2 (COVID-19) infection may be considered an evolutionary selective disease, which will contribute to the present-day world global distribution of the human A and B blood groups that according to (Springer and Wiener, 1962) has predominantly arisen in connection with blood group-related life-threatening diseases over millions of years. The synthesis of the blood group AB enables the strongest contact with a pathogen and molecularly precluding any isoagglutinin activity, making this group the least protected and the smallest among the ABO(H) blood groups. In contrast, individuals

with blood group O(H), which are prone to many other infections, especially to cholera disease, despite extensive historical cholera pandemics (Echenberg, 2011; Mutreja *et al.*, 2011; Chowdhury *et al.*, 2017) have survived all infectious diseases in an immunological balance with many pathogens as the largest blood group worldwide. These people rarely develop severe disease in blood group A/B-related infections. In fact, they maintain the anti-A/Tn cross-reactive and anti-B complement-dependent isoagglutinin activities, which are exerted by the polyreactive, nonimmune immunoglobulin M (IgM) (Arend, 2018b; Arend, 2017), regarded as the humoral spearhead of innate immunity and first line of defense. However, during SARS-CoV-2 pandemic a large number of infected people remains asymptomatic, and it might be speculated that especially blood group O individuals for an unknown period of time remain pathogen carriers and belong to the main drivers of the pandemic.

Proposed Adhesion, Response and Autoimmune Response

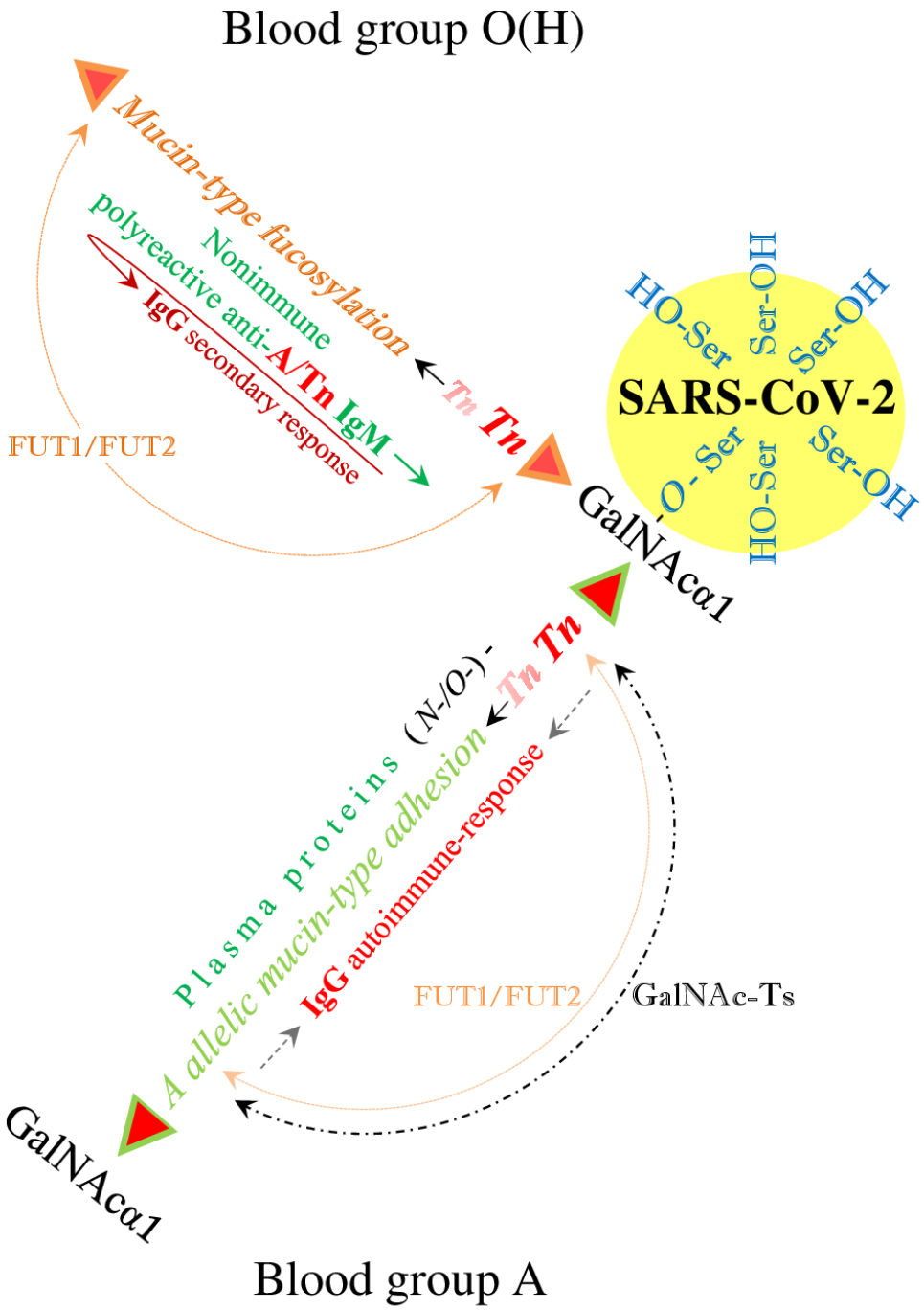

Figure 2.

Figure 2.

The ABO(H) phenotype formation occurs on both the cell surfaces and plasma-proteins (Arend, 2016). The intermediate A-like/Tn structure has been elongated and/or replaced by mucin-type, blood group O(H) and A-determining epitopes. In blood group O(H), which solely neutralizes the anti-H isoagglutinin activity and binds the virus alone by hybrid FUT1/FUT2 or H-type antigen formation, the anti-A isoagglutinin activities remain unaffected. While in the 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), adaptive IgG arises in a secondary response against the hybrid A-type structure exerting autoreactivity. This figure was constructed according to Figure 2 in a previous article (Arend, 2018b), in which this mechanism may be similarly utilized by a non-viral pathogen, such as the protozoan parasite *Plasmodium falciparum*.

Central immunological position and evolutionary cross-over point of the human histo (blood group) O(H)

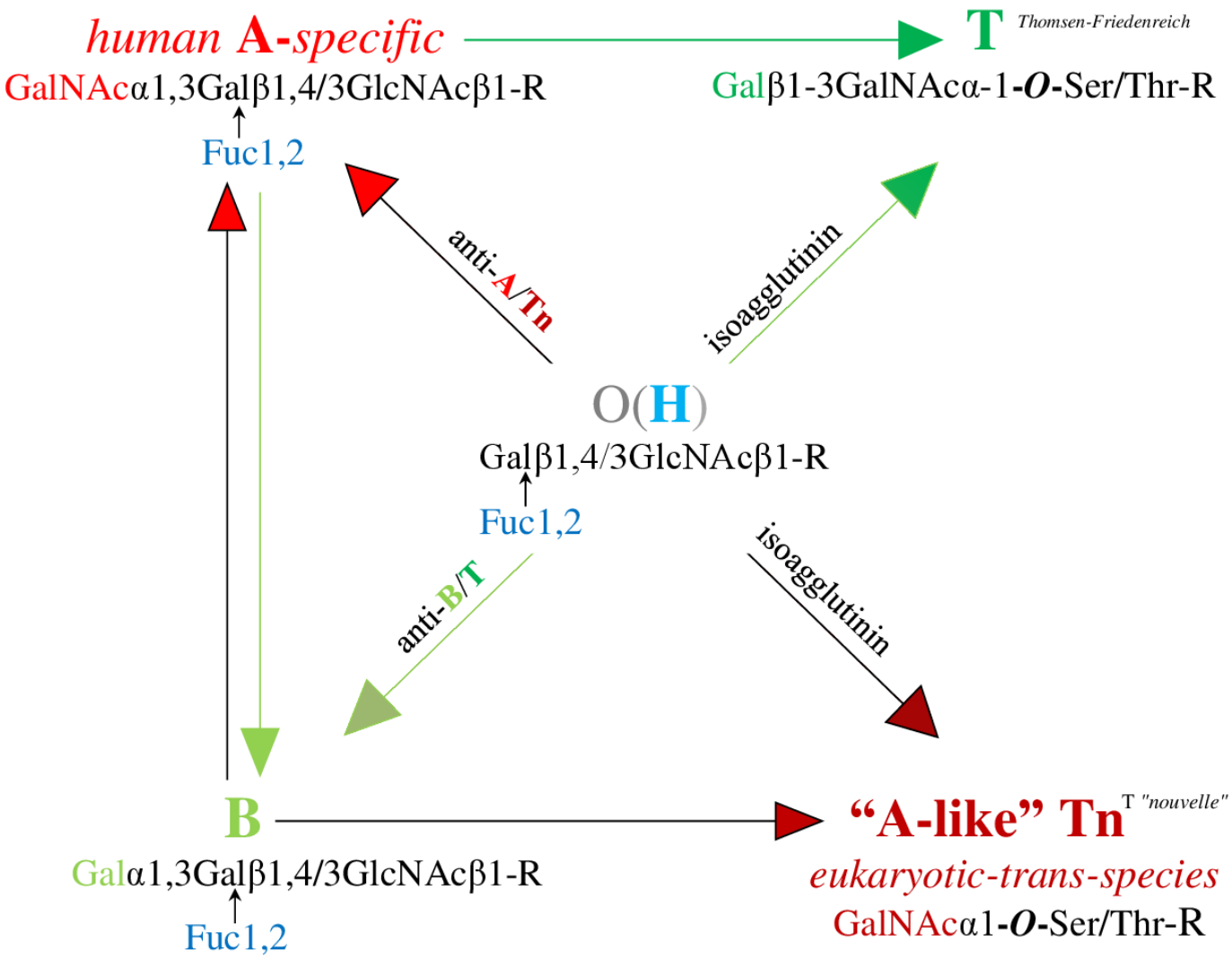

Figure 3.

Figure 3.

The central immunological position of the blood group O(H) is evident in its comprehensive production of "natural" antibodies against all of the mature A and B glycans and their cross-reactive developmental structures Tn and T. The human A-specific (A-allelic) glycosylation and the trans-species "A-like"/Tn formation are developmentally connected via the formation of cross-reactive anti-A/Tn isoagglutinin. According to Hofmann (Hofmann *et al.*, 2014) blood O(H) sera bind to both Tn and T antigens, and the anti-A isoagglutinin levels in blood group O(H) and blood group B sera are associated with the anti-Tn antibody, which does not react with blood group B red cells or T glycoconjugates. By contrast, the anti-B antibodies of blood group A sera and of blood group O(H) sera bind to B and T glycoconjugates but not to A or Tn glycoconjugates. This selective cross-reactivity of isoagglutinins with Tn and T antigens has been explained by the authors through the phenotype-specific terminal moieties; the terminal N-acetylgalactosamine is shared by A and Tn antigens, and the terminal galactose is, although with a different configuration, shared by B and T antigen. This figure was constructed by Arend (2017) and cited in Arend (2018b; 2018a)

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