

Central position of the human blood group O and phenotype-determining enzymes in growth and infectious disease

Peter Arend

Abstract

The human ABO(H) blood group phenotypes arise from the evolutionarily oldest genetic system found in primate populations, but they originated in critical molecular complementarity with distinct eukaryotic and prokaryotic pathogens, while the development of non-O(H) phenotypes is associated with impaired formation of adaptive and innate immunoglobulin specificities due to clonal selection and phenotype formation in plasma proteins. Indeed, compared with individuals with blood group O(H), blood group A individuals not only have a significantly higher risk of developing certain types of cancer but also exhibit high susceptibility to malaria tropica or infection by *Plasmodium falciparum*. Thus, the phenotype-determining blood group A glycotransferase(s), affecting the levels of anti-A/Tn cross-reactive immunoglobulins in phenotypic glycosidic accommodation, might also mediate adhesion and entry of the parasite to host cells via trans-species O-GalNAc glycosylation of abundantly expressed serine residues, arising throughout the parasite's life cycle, while excluding the possibility of antibody formation against the resulting hybrid antigen. In contrast, human blood group O(H), lacking this enzyme and providing the molecular mechanism of protecting human reproduction, is indicated to confer a survival advantage regarding the overall risk of developing cancer, and individuals with this blood group rarely develop life-threatening infections involving evolutionarily selective malaria strains.

Keywords: blood group O position; complementary pathogen; phenotypic glycosidic accommodation; hybrid Tn antigen; nonimmune immunoglobulin M (IgM)

Introduction

The human gut microbiome has been a subject of comprehensive research for decades, and numerous reviews have discussed various aspects of host-microbe interactions in the context of health and disease. In terms of host genetics and immunity,^{1, 2, 3} "naturally occurring" immunoglobulins arise from various sources via different molecular pathways, and the ABO blood group is among the genetically determined host factors that modulate the composition of the human intestinal microbiota.⁴ Specifically, the microbiota of blood group B individuals differs from those of individuals with non-B antigen phenotypes, for example, showing higher diversity in the *Eubacterium rectale* and *Clostridium leptum* groups. However, when the adaptive production of anti-blood group B-reactive immunoglobulins, which occurs in White Leghorn chickens fed a diet containing *E. coli* O86:B7 lipopolysaccharide,⁵ was demonstrated for the first time to occur spontaneously in humans,⁶ this form of isoagglutinin production was documented exclusively for the histo (blood) group O(H). Bacterial endotoxins non-specifically stimulate the formation of all immunoglobulins, but prokaryotic blood group A/B-like antigenic structures appear to induce cross-reactive anti-A/B immunoglobulin^{7, 8, 9} that arise in neither blood group A nor B individuals but occur predominantly or exclusively in blood group O(H) due to clonal selection. Consequently, in patients suffering from ulcerative colitis causing increased enteral absorption, the minimally and likely non-specifically elevated levels of anti-B-reactive 7S (IgG) and 19S (IgM) in blood group A plasma were found to remain within the normal range; additionally, a statistically significant increase in anti-B-reactive IgG and IgM immunoglobulins involving less-pronounced, asymmetrically cross-reactive anti-A-specific IgG was detected exclusively in blood group O(H) plasma, and the IgG/IgM quotients showed predominance of the IgG class (Figure 1). These early, limited observations are consistent with later investigations performed with current experimental tools. For example, Stussi *et al.*¹⁰

detected anti-A/B cross-reactive IgG in 89% of blood group O(H) sera and anti-B-reactive IgG in 4% of blood group A sera, and vaccination with pneumococcal polysaccharides exclusively elicited anti-A/B cross-reactive IgG but did not affect pre-existing anti-A/B-reactive IgM levels.¹¹ While the danger theory¹² suggests that there is no adaptive immunity without innate immunity, the bulk of human immunity is not acquired during a single human lifetime but is considered to arise predominantly from evolutionary memory and survival mechanisms. Thus, an inborn origin has been postulated to explain isoagglutinin production in non-O blood groups.^{13, 14} In addition to adaptive, cross-reactive anti-A/B production, which is mainly restricted to blood group O(H) individuals, the majority of anti-A/B immunoglobulins, especially the classic complement-binding anti-A and anti-B-reactive isoagglutinins, measured between 22 and 24°C are not controlled by clonal selection and primarily arise independent of any blood group. These immunoglobulins result from a polyreactive, non-immune, germline-encoded IgM molecule that is released after germ cell maturation and cell renewal, and undergoes phenotype-specific glycosidic accommodation of plasma proteins in the non-O blood groups.^{13, 15} It is proposed that depending on the quality of glycosylation, the degree of glycosylation of an immunoglobulin is inversely proportional to its reactivity. While any phenotype-directed auto-reactivity, primarily exerted by germline encoded antibodies, may automatically be neutralized during the course of phenotype formation in normal condition, the dynamic glycosylation of immunoglobulins plays a key role in physiology and mainly occurs via *N*-linkages. Nevertheless, a proteomics analysis of *O*-GalNAc glycosylation in human serum identified 407 intact *O*-GalNAc glycopeptides from 93 glycoproteins¹⁶. Thus, in blood group A and B individuals, phenotype-determining GalNAc- or D-Gal glycosylations of plasma proteins are, aside from prevailing *N*-glycosylations, hypothetically associated with mucin-type formation, utilizing *O*-linkages to functional

serine/threonine or tyrosine residues from the Fc region of the ancestral IgM molecule¹⁷. The terminal serine appears to be the crucial structure,¹⁸ and any reduction or exclusion of IgM anti-self reactivity thereby achieved necessarily impairs adaptive and innate defense activities.¹⁵ The key molecule in this phenotypic accommodation might be α 2-macroglobulin, which is considered to be an evolutionarily conserved arm of the innate immune system.¹⁹ α 2-Macroglobulin is functionally strongly connected to the structurally related IgM molecule, as becomes evident from adhesion of the parasite *Plasmodium falciparum* (*P. falciparum*) to the host cell surface in severe malaria disease,²⁰ and exhibits ABO(H) blood group reactivity in strict correlation with the cell surface.^{21, 22} Consequently, in blood group O(H) individuals, non-immune and adaptive anti-A and Tn-cross-reactive IgM/IgG, whose levels are unaffected, are still involved in internal and external immune defense. Indeed, the binding of non-immune IgM to a blood group A-like or Tn antigen might, similar to a primary immune response, initiate a secondary response involving the formation of anti-A/Tn cross-reactive IgG, with T cell and natural killer (NK) cell activation,¹⁵ which is affected by glycosidic, phenotypic accommodation in non-O blood groups. This appears to be a general principle that not only may contribute to the increased susceptibility of non-O blood groups to cancer development but even explains the varying susceptibilities of the different ABO(H) phenotypes to special infectious diseases via trans-species molecular complementarity, through which intriguingly, malaria strains might even interfere with cancerous growth.

Molecular relationship of human ABO(H) blood group phenotype evolution and development to growth and malaria infections

Clonal selection and the principle of glycosidic, phenotypic accommodation explained above have been postulated to contribute to the increased risk of human blood group A individuals

developing different types of cancer,¹⁵ and the naturally occurring anti-A-reactive isoagglutinins and anti-Tn-cross-reactive antibodies clearly interact with tumor-associated *O*-glycan structures produced in pancreatic cancer.²³ In a recent cancer risk cohort study, Sun *et al.*²⁴ described a statistically significant risk of stomach cancer and pancreatic cancer in blood group A individuals compared with blood group O(H) individuals, while kidney cancer risk was inversely associated with blood type AB. A comprehensive study by Vasan *et al.*²⁵ showed positive associations in blood group A individuals with cancer of the pancreas, breast, salivary glands, mouth, stomach and chronic lymphatic leukemia and in blood group B individuals with cancer of the corpus uteri and the bladder; however, inverse associations were observed in blood group A individuals for pharyngeal cancer, esophageal adenocarcinoma, and small intestinal cancer and in blood group B individuals for pleural mesothelioma and myelomas. In two smaller studies, regarding the O/O and A/A genotypes, the above positive associations became even clearer in both cancer of the stomach²⁶ and that of the pancreas²⁷ and were finally considered to be established. Thus, blood group A individuals might be burdened with an overall increased risk of developing cancer compared with individuals exhibiting blood group O(H), which is currently thought to confer a survival advantage compared with non-O blood groups.^{28, 29}

Considering that a species barrier may be overcome by interspecies glycosylations³⁰ and ABO(H) glycotransferases accomplish the cross-species transmission of *O*-glycans in infectious diseases,³¹ the proposed principle of glycosidic, phenotypic accommodation may explain the pronounced susceptibility of non-O blood group individuals to the life-threatening infections characteristic of classic malaria tropica, which is caused by *P. falciparum*.³² While malaria tertiana or infection by *P. vivax* is the best-documented type of malaria, *P. falciparum* causes the most severe and frequently encountered type of the disease. For both malaria types, the risk of

developing malaria is strongly associated with phenotype, but the available systematic reviews and intensive meta-analyses are restricted to malaria tertiana and the Duffy blood group system, which includes a genetically determined special *P. vivax* receptor. This Duffy-Antigen Receptor for Chemokines, or DARC, is a complex, polyfunctional glycoprotein that, as a chemokine receptor, binds a variety of chemokines secreted by cells during inflammation, such as C-X-R (acute inflammation chemokine), C-C (chronic inflammation chemokine) and the IL-8 (interleukin 8).^{33, 34} DARC carries the 6 different Duffy blood group antigens: Fy^a, Fy^b, Fy³, Fy⁴, Fy⁵ and Fy⁶.³⁵ The Duffy-positive phenotypes Fy (a+b+), Fy (a+b-) and Fy (a-b+) are found mainly in Caucasian and Asian individuals, while the Fy^a allele likely represents the globally most prevalent allele.³⁶ Fy^a individuals are highly susceptible to infections by *P. vivax*, whereas the Duffy-negative phenotype Fy (a-b-) group shows strong resistance and is almost exclusively limited to individuals of African descent.³⁴ Consequently, this type of malaria is extremely rare in Africa. While Duffy-positive individuals are susceptible to *P. vivax* infections and human blood group A,³⁷ B and AB-individuals³⁸ are highly susceptible to severe infections by *P. falciparum*, the DARC protein appears to exhibit marked growth-regulating activity in different types of cancer,^{39, 40} in contrast to the cancer susceptibility of blood group A. This effect was explained by suppression of the activation of the transcription factor STAT3 (signal transducer and activator of transcription 3) through inhibition of CXCR2 (a chemokine adaptor protein) signaling.⁴¹ The functional or structural relationships of the DARC protein to the non-immune IgM or isoagglutinins of the ABO(H) blood group system are unknown. Natural anti-Duffy-reactive IgM occurs extremely rarely, and the naturally occurring anti-Duffy antibody arises almost exclusively as an adaptive IgG, mainly caused by repeated infections and incompatible blood transfusions.

The susceptibility of non-O blood group individuals to the infection by *Plasmodium falciparum* resides in molecular complementarity between the host and parasite

Infection by this parasite occurs mainly in tropical and subtropical areas of South America, Africa, and southeast Asia. These infections appear to be limited to certain ethnic groups,⁴² although episodes of global distribution involving life-threatening diseases are a widely discussed problem.⁴³ Statistically significant life-threatening infections are diagnosed in blood group A,³⁷ B, and AB⁴⁴-individuals compared with those with blood group O(H), although in areas where this type of malaria is endemic, blood group O(H) individuals may represent the largest group of gametocyte carriers, who sometimes even suffer from mild disease.⁴³ *P. falciparum* differs from the other human malaria species in that infected RBCs do not remain in the circulation for the entire life cycle; instead, when young parasites mature to the trophozoite stage, infected RBCs adhere to endothelial cells in the microcirculation.⁴⁵ This phenomenon, termed “sequestration”, appears to be another characteristic of life-threatening disease resulting from *P. falciparum* infection, in addition to RBC rosette formation, and occurs rarely in infections involving the "non-sequestering" *P. vivax*, *ovale* and *knowlesi*.

In cooperation with the host's nonimmune IgM,⁴⁶ the parasite *P. falciparum* binds by the PfEMP1 protein (Plasmodium falciparum Erythrocyte Membrane Protein 1) to RBC surfaces via the common *Duffy Binding-Like (DBL)* domain, and binds statistically significantly increased to the RBC of non-O blood groups⁴⁷ when compared with those of group O. However, because the RBC membrane lacks detectable expression of the blood group A- and B-determining transferases, it is assumed that the binding between host and pathogen is basically accomplished by plasma proteins and soluble enzymes. Indeed, soluble enzymes, which accomplish the formation of soluble blood group A/B structures and phenotype formation of plasma proteins¹⁵, may also perform the attachment of the inoculated plasmodium sporozoites to the cell

membranes of the host. A functional soluble blood group A-transferring serum transferase has been described by Nagai et al.,⁴⁸ who transferred UDP-GalNAc to blood group O RBC in *vitro*. Although a transfer of this molecule to a pathogen has never been reported before, the coincidence of statistically significant occurrence of life-threatening infections by *P. falciparum*, with the synthesis of a common acceptor protein or peptide for blood group A and B-determining transferases in non-blood group O populations, highly suggest that trans-glycosylation of blood group A and B glycans plays a key role in this disease. Breaking the species barrier, trans-glycosylation and trans-peptidation may be the fundament in development of infectious diseases; according to Varki and Lowe³⁰, viruses are performing the glycosylations of their proteins by utilizing the host cell machinery, and pathogens invading multicellular animals, may decorate themselves with structures that appear to be identical to those found on their host cell surfaces; Kreisman et al. argued that a pathogen seeking to bind to cell membranes of the host may first encounter the specific glycans attached to soluble mucinous structures.⁴⁹ In fact, while mucin-type O-GalNAc glycosylation likely plays the major role in cell adhesions⁵⁰, soluble blood group A and B-determining enzymes hypothetically initiate the synthesis of adhesion molecules via heterologous mucin-type O-glycosylation of the parasite's serine repeat antigen (SERA); that is a serine-rich protein providing numerous N- and O-glycosidic sites. This protein primarily appears during the intraerythrocytic stages of the parasite, while serine residues are expressed at all stages of the parasite' life cycle, and even occur on the surface of inoculated sporozoites, which are proteolytically processed by a serine protease.⁵¹ The SERAs are encoded from a multigene protease family, common to all *Plasmodium* species^{52, 53} but occurring in different types, from which the serine type SERAs-SERA5 and cysteine type SERA-SERA6 show the highest levels in *P. falciparum*^{54, 55}.

According to a recent study, SERA5 has been demonstrated to have no enzymatic role⁵⁶ during the blood-stage growth of *P. falciparum*, and although obviously regulating the kinetics and efficiency of malaria parasite invasion and egress from host erythrocytes, neither SERA5 function nor the role of its processing appear to be completely understood⁵⁷. Nevertheless, in view of the strong susceptibility of the human blood group A organism to infection by *P. falciparum*, SERA5 highly suggests to even function as an acceptor in enzyme-substrate competition between host and parasite in mucin-type *O*-GalNAc glycosylations. Again, as viruses are performing the glycosylations of their proteins by utilizing the host cell machinery³⁰, plasmodium species may utilize the same way (Figure 2). Without questioning the established role of RIFINs^{58, 59, 60, 61}, which are discussed to be provided by the pathogen alone, a functional blood group A-determining plasma transferase transferring the blood group A glycan, may indicate an additional and/or more complex pathomechanism, involving a trans-species A-like, Tn-mucin-type GalNAc-1-*O*-Ser/Thr-R structure, representing a classical adhesion molecule that promotes glycan elongations and the binding between parasite and host. Finally, the human blood group A-specific α 1-3-N-acetylgalactosaminyltransferase and blood group B-specific α 1-3-galactosyltransferase, expressed by plasma proteins might, together with serine/threonine kinases produced by *P. falciparum*, provide the essential metabolic condition for heterologous synthesis of mucin-type adhesion proteins and GalNAc-1-*O*-Ser/Thr-R glycosylation in the blood group A, and Gal-1-3GalNAc-1-*O*-Ser/Thr T-R glycosylation in the blood group B. The proposed glycosidic accommodation of plasma proteins^{14, 15} is not a lock-and-key event but a dynamic process, dominated by continuous synthesis of α 2-macroglobulin and its functional synergism with the structurally related non-immune IgM; this molecule being engaged in the adhesion process via its Fc region⁶² and *O*-glycosylation^{14, 15} of germline-serine-residues¹⁸,

obviously cannot induce rosetting on its own,²⁰ whereas α 2-macroglobulin crosslinks multiple PfEMP1 molecules and, thus, is an integral component of rosette formation. The differences in the life cycle of the parasite during uncomplicated malaria in blood group O(H) individuals and life-threatening disease in blood group A and B individuals remain unknown. The complex infection process is presumably initiated by heterologous glycosylation, which has long been considered the major carbohydrate modification in the intraerythrocytic stage of *P. falciparum*,⁶³ and *O*-glycosylation appears to be the major form,⁶⁴ whereas the role of the AB/(O/H) phenotypes has largely been ignored. The metazoan/eukaryotic lineage, which comprises the evolutionarily first protein glycosylation by GalNAc via *O*-linkages on peptides displaying serine/threonine motifs, is characterized by mammalian embryonic stem cell fidelity to initiate and complete germ cell maturation. When breaking the species barrier, this glycosylation may promote the asexual reproduction of *Plasmodium* merozoites, which involves immature gamete formation, and may even explain the attachment of infected to uninfected RBCs. Indeed, rosette formation occurs predominantly with human blood group A RBCs,^{37, 47} while incomplete formation in blood group O(H) RBCs, as molecularly explained by Moll et al. (1915),⁶⁵ may be associated with weak disease. Serine/threonine and tyrosine kinases are exported by *P. falciparum*^{66, 67}, and the infected RBC membrane exerts serine transferase activity, representing a potential anti-malaria drug target during the asexual intraerythrocytic stage.^{67, 68} Thus, SERA, which was detected decades ago,⁶⁹ is accepted as a putative antigen precursor, while heterologous *O*-GalNAc glycosylation, which most likely utilizes trans-species-compatible serine positions on the surface of plasmodium sporozoites, might explain the preferred binding of special *Plasmodium* strains. In conclusion, the pronounced susceptibility of blood group A individuals to severe malaria³² suggests the formation of a hybrid Tn-reactive structure,

providing another molecular definition of a potential immunological (therapeutic) target, while blood group O(H) individuals, who are unable to complete this self-destructive, likely transient, hybrid connection further maintain both natural non-immune anti-A/Tn IgM and IgG cross-reactive antibodies against this connection (Figure 2).¹⁵ Molecularly incomplete connections arise in the blood group O(H) phenotype individual likely via non-specific, blood group A and B-independent glycans. Moreover, analyses of AO exons and introns in individuals with an “A-to-weak B phenotype” have revealed a novel O1v-A2 hybrid allele leading to missense mutations in A-transferases and/or transferees, whereas unusual O alleles, including O2, at the ABO(H) locus may be implicated in unexpected blood group phenotypes.⁷⁰ Thus, the O(H) phenotype is no longer considered a genetic entity^{71, 72} but is sporadically contaminated with weak A alleles, which, when exerting weak A-determining enzyme activities, may promote severe malaria infection. Notably, weak A-determining enzyme activities manifest as an O(H) serological blood group in patients, making true statistics impossible and potentially explaining the various conflicting results demonstrated by multiple studies.

How malaria infection might interfere with early cancer development

Heterologous A-like *O*-GalNAc glycosylation, most likely occurring upon exposure of the substrate and the transfer enzyme of the host to a surplus of serine residues from *Plasmodium falciparum*,^{66, 59, 57} might interfere with the early steps of cancer development through enzyme-substrate competition with cancerous GalNAc α 1-*O*-Ser/Thr glycosylation, although this hypothesis appears to not be applicable to all malaria strains. Actual therapeutic concepts based on the special histochemistry of placental malaria and parasite-derived metabolites⁷³ are developed without consideration of the ABO(H) blood group system, whereas *P. falciparum* and

P. vivax potentially employ different ABO(H) acceptors: according to a study by Lo *et al.* (2015)⁷⁴ addressing the distribution and prevalence of *P. vivax* and *P. falciparum* infections investigated in parallel in Duffy blood group patients, the reactivities of Duffy-positive individuals are more similar to those of group O than group A. Indeed, despite their established susceptibility to *P. vivax* infections, Duffy-positive individuals appear to be less susceptible than Duffy-negative individuals to infection by *P. falciparum* and further share the superiority of group O in controlling the development or inhibition of cancer. According to a recent study, growth inhibition is exerted by unspecified malaria strains on various types of cancers, and the worldwide malaria incidence and cancer mortality appear to be inversely associated.⁷⁵ An exception to this pattern is observed for Burkitt lymphoma, which primarily occurs in regions where *P. falciparum* in association with Epstein-Barr virus infections⁷⁶ is endemic.⁷⁷ However, data from highly endemic countries in Africa were not included in the underlying studies. Thus, the impact of endemic malaria on cancer mortality in these analyses hypothetically reflects *P. vivax* malaria, which prevails outside of Africa, rather than *P. falciparum* malaria, which prevails within Africa. The authors of these studies explained this phenomenon based on the functions of pathogen-associated molecular patterns (PAMPs). Specifically, *Plasmodium* PAMPs, observed in all four species of human malaria parasites (*P. vivax*, *falciparum*, *ovale* and *malariae*),⁷⁸ trigger the host immune response against cancer via pattern recognition receptors (PRRs).⁷⁹ However, because these studies were performed in geographical areas that are natural habitats of Duffy-positive people, who harbor the globally most prevalent allele Fya,³⁶ the lower numbers of tumor diseases may also reflect DARC protein activities. Moreover, blood group O(H), which is commonly observed within Caucasian populations and is associated with a reduced overall risk of developing cancer, may come into play. Consequently, the virtual genotype O/O Fy

(a+b+) confers the lowest risk but does not occur alone in any population, while the A/A Fy (a-b-) genotype carries the highest risk, and A/A Fy (a+b+) and other ABO(H)/Duffy allelic mixtures balance these risks. Thus, the data reported in one previous study⁷⁵ together with the above data reflect the mixed impact of different genotypes, resulting in at least two blood group systems associated with a risk of cancer development: the ABO(H) and Duffy groups. The risk of developing any disease is rarely associated with a single phenotype, and given the lack of reliable data concerning *P. falciparum* and *P. vivax* infections and their outcomes in blood group A and O(H) individuals and/or genotypes specified in parallel with Duffy groups, any further molecular biological explanations for the differing susceptibilities of the Duffy Fya phenotype and blood group A individuals to *Plasmodium* infections and cancer remain speculative.

Induction of infectious diseases occurs via molecular complementarity between host and pathogen

Regardless of potential allelic interactions or cooperation, the process of *P. falciparum* merozoite invasion, most likely involving SERA5, shows an intriguing connection to early metazoan growth processes, which appear to be dominated by trans-species O-GalNAc1-O-Ser/Thr-R glycosylation. Under normal conditions, this glycosylation is followed by rapid deglycosylation and may further be followed by the specific glycosidic construction of the A, B and AB phenotypes in humans¹⁵ after zygote formation, with the exception of blood group O(H). These phenotypes arise from the evolutionarily oldest genetic system found in primate populations⁸⁰ but always occur in critical complementarity with the metabolism and recognition tools of distinct eukaryotic and prokaryotic pathogens. The species-independent ABO gene polymorphism has been extensively analyzed in primates,^{81, 82} but an understanding of the ramifications of this polymorphism has been elusive.⁸³ Consequently, reports describing the

susceptibility of different ABO(H) blood groups to viral and bacterial infections are controversial. Nevertheless, while intestinal fucose functions as a mediator of host–microbe, hybrid symbiosis⁸⁴, there are established susceptibilities of the human blood group O(H) phenotype to infection with *Helicobacter pylori* (*H. pylori*)⁸⁵ and specific types of cholera infections.^{86, 87} Similar to malaria tropica, the adhesion of these pathogens to host cells appears to be accomplished through trans-species glycosidic accommodation, which in blood group O(H) primarily means synthesis of the precursor structures H and Se via human-specific α 1,2 (FUT1/FUT2) L-fucosylation. In *H. pylori* infections, the synthesis of these structures is modulated by α L-1,3 (FUT1/FUT3) fucosylation and the formation of the different Lewis group structures, which together with H and Se molecules, characterize the *O*-side chain of the *H. pylori* lipopolysaccharide and mucin-type adhesion proteins.^{88, 89} In cholera infection, a similarly complex pathogenesis dominated by functional mucin-type adhesion molecules is initiated by the *receptor-destroying enzyme*, a mixture of hydrolases discovered by Burnet and Stone⁹⁰ as early as 1947. This *receptor-destroying enzyme* is governed by a neuraminidase associated with the secretion of adhesion proteins⁹¹ that cause pan-agglutination and RBC rosette formation,⁹² which is known as the Hübener-Thomsen Friedenreich phenomenon.⁹³ The adherence of *Vibrio cholerae* to isolated rabbit brush border membranes⁹¹ of human RBCs and the lymphoid follicle epithelium of the intestine is (depending on the cellular HA type) inhibited by L-fucose.^{94, 95} Therefore, the enzymatic precursors or FUT1/FUT2 activities of blood group O(H) patients are assumed to be involved in trans-species sugar transfer to a Gal- β 1-R (Oh) acceptor that is hypothetically expressed by the pathogen(s) and virtually transformed into a transient heterologous O(H) epitope. Consequently, in addition to modulating Lewis structures, the blood group O(H) individual will neither produce an adaptive anti-H-reactive antibody nor exhibit a

natural, nonimmune anti-H antibody against its own epitope under normal conditions (Figure 3); indeed, significant production of anti-H antibodies is limited to the extremely rare O(h) *Bombay*-type individual, lacking the normal, human-specific FUT1/FUT2 fucosylations⁹⁶ and respective fucosylations of plasma proteins.⁹⁷ At present, the lowest prevalence of blood group O(H) worldwide occurs in the Ganges delta, where cholera has been endemic for centuries.⁸⁶ However, despite extensive historical cholera pandemics,^{98, 99, 100} which, like malaria, contribute to the global distribution of ABO(H) blood groups in the human population, as well as complex infections with *H. pylori*, blood group O(H) providing the molecular mechanism of protecting human reproduction,⁹⁷ and offering the widest functional flexibility in adaptive and germline-encoded innate immunity, has survived as the most frequently occurring blood group within the ABO(H) blood group system.¹⁰¹ Although Duffy Fya represents the most common allele worldwide,³⁶ blood group O(H) is superior in controlling both cancer growth and life-threatening infections involving the most frequently encountered plasmodium species.

Conclusion

"Naturally occurring" immunoglobulins arise from various sources via different molecular pathways.⁸ While clonal selection protects mammalian species from the formation of environmentally induced adaptive, self-reactive immunoglobulins, the human blood group A, B and O(H) phenotypes additionally exclude the presence of a self-reactive, germline-encoded non-immune IgM through identical glycosylation of cell surfaces and plasma proteins.^{14,15} Consequently, phenotype-specific susceptibility to infection by a special pathogen necessarily reduces or excludes natural immunological protection. This implies that the phenotype-determining glycotransferase might play the first role in determining the susceptibility of an

individual to infection by a special pathogen; this enzyme both establishes contact with a complementary acceptor of the pathogen and reduces or excludes the presence of a phenotype-specific antibody through glycosidic exclusion and/or accommodation of plasma proteins.^{14,15} Again, the observations accumulated in the literature suggest that an infectious disease may be initiated via phenotypic accommodation between host and pathogen. For example, the ABO(H) phenotype-determining transferase of a host transfers its sugar to an ABO(H) complementary acceptor of a pathogen, such as SERA from *Plasmodium* species, or a Gal- β 1-R (Oh) residue, as hypothetically expressed by *H. pylori* and *Vibrio cholerae*. Thus, in the case of severe malaria in individuals with human blood group A or *H. pylori* infection and cholera disease in phenotype O individuals, the contact between the host and pathogen appears to be initiated through "destructive cooperation" between heterologous-complementary carbohydrates and/or peptides. This implies that anti-ABO(H)-reactive immunoglobulins remain basically engaged in the control of those internal growth processes, from which most of them arise. Nevertheless, these immunoglobulins may non-specifically or cross-reactively protect the organism from environmental infections and pathogens that are not involved in their production, a phenomenon characteristic of the polyreactive defense proteins of invertebrates. The anti-A/anti-Tn-cross-reactive hemagglutinin emerging from the coat proteins of fertilized eggs of *Helix pomatia*¹⁵ and lectins from other snails agglutinate *Staphylococcus aureus*, *Escherichia coli*, *Listeria* and several *Salmonella* species. This effect is likely due to N-acetyl-D-galactosamine residues¹⁰² because all bacteria utilize this sugar in different metabolic pathways, which do not necessarily lead to complete antigenic structures. Thus, the central immunological position of the human histo (blood) group O(H) remains evident in its comprehensive presentation of both nonimmune IgM and adaptive IgM/IgG antibodies. These antibodies are mainly directed against all non-O

blood groups, involving their cross-specific developmental and/or "aberrant" structures²³ (Figure 3), as early metazoan eukaryotic *O*-glycans, T (Thomsen-Friedenreich)¹⁰³ and Tn (T nouvelle)¹⁰⁴ antigens have been identified. These ancestral glycans arising from *O*-glycosylations, which are used (with similar peptide backbones) by lower metazoans, such as mollusks and the fruit fly *Drosophila melanogaster*;^{105, 106} moreover, in the snail *Helix pomatia*, they are associated with the release of a hexamerically¹⁰⁷ structured Tn-complementary hemagglutinating defense protein. In 1973, Hammarström demonstrated that 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,¹⁰⁸ giving rise to speculation regarding an evolutionary relationship with the mammalian non-immune anti-A-reactive IgM molecule. While the germline of *Helix pomatia* appears not to be burdened with A/B phenotypic accommodations, similar to the polyreactive ancestral IgM of human blood group O(H), this species and other snails never develop cancer. An even stronger immunity, involving a clinically relevant anti-H-reactive, complement-binding IgM and most likely higher anti-A/Tn levels than in blood group O(H), is exerted by the "real" blood group O or *Bombay*-type O(h) (h/h; se/se), according to a mutational meltdown of the H and Se gene functions on chromosome 19 (encoding the α 1,2 L-fucosyltransferases (FUT1/FUT2)). However, the extremely small population size of the classic *Bombay* type suggests an effect on reproductive health⁹⁷ and demonstrates a negative evolutionary role. While the background of these mutations has been discussed controversially and studies on the functions of α 1,2 L-fucosyltransferases in murine fertility¹⁰⁹ may not be extrapolated to human phenotype development, primates use different pathways for critical fucosylation events,¹¹⁰ and human α 1,2 L-fucosyltransferase genes are exclusively responsible for the expression of ABO antigens.¹¹¹ Indeed, normal blood group O(H) formation, based on α 1,2 L-fucosylations, which

protect human reproduction, emphasizes the central position of this blood group in the evolution of primates because it represents the most frequent blood group within the ABO(H) system worldwide. Furthermore, this blood group may confer a general survival advantage resulting from superior complex immunity, in which human-specific non-immune anti-A-reactive IgM or isoagglutinin appears to be an authentic complementary protein to the trans-species, developmental Tn epitope.¹⁵ This complement-binding, polyreactive protein may exert its immunological effect during ABO(H)-incompatible blood transfusions, mirroring its role in internal defense processes. Moreover, similar to lectins, this protein might non-specifically bind prokaryotic pathogens and prevent the interference of malaria plasmodia with early developmental *O*-GalNAc glycosylation processes.

References.

1. Rooks, M. G. & Garrett, W. S. Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* **16**, 341–52 (2016).
2. Vatanen, T. *et al.* Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. *Cell* **165**, 842–853 (2016).
3. Kurilshikov, A., Wijmenga, C., Fu, J. & Zhernakova, A. Host Genetics and Gut Microbiome: Challenges and Perspectives. *Trends in Immunology* (2017).
doi:10.1016/j.it.2017.06.003
4. Mäkiyuokko, H. *et al.* Association between the ABO blood group and the human intestinal microbiota composition. *BMC Microbiol.* **12**, 94 (2012).
5. Springer, G. F., Williamson, P. & Brandes, W. C. Blood Group Activity of Gram-Negative Bacteria. *J. Exp. Med.* **113**, 1077–93 (1961).
6. Arend, P. & Fehlhaber, G. Varying influence of increased enteral antigen absorption on the behavior of “natural” antibodies in O and A blood group subjects. Comparative blood group serological studies on patients with ulcerative colitis and healthy persons [Article in German]. *J. Mol. Med. (Klinische Wochenschrift)* **47**, 535–541 (1969).
7. Gonano, F., Modiano, G., and de Andreis, M. Relationships between the Somatic Antigens of *E. coli* O86 B:7 and Blood Group A and B Substances. *Vox Sang.* **6**, 683–691 (1961).
8. Arend, P. Observations on different origins of “naturally-occurring” antibodies. *Eur J Immunol* **1**, 398–402 (1971).
9. Obukhova P, Korchagina E, Henry S, B. N. Natural anti-A and anti-B of the ABO system: allo- and autoantibodies have different epitope specificity. *Transfusion* **52**, 860–9 (2012).
10. Stussi, G. *et al.* Isotype-specific detection of ABO blood group antibodies using a novel flow cytometric method. *Br. J. Haematol.* **130**, 954–963 (2005).
11. Sauerwein Wolfram W, Binder KM, Eibl-Musil, CJ, Wolf HM, F. M. Pneumococcal Polysaccharide Vaccination Elicits IgG Anti-A/B Blood Group Antibodies in Healthy Individuals and Patients with Type I Diabetes Mellitus. *Front Immunol.* **14**, 493 (2016).

12. Matzinger, P. Tolerance, Danger, and the Extended Family. *Annu. Rev. Immunol.* **12**, 991–1045 (1994).
13. Arend, P. & Nissen, J. A-specific autoantigenic ovarian glycolipids inducing production of “natural” anti-A antibody. *Nature* **269**, 255–7 (1977).
14. Arend, P. ABO (histo) blood group phenotype development and human reproduction as they relate to ancestral IgM formation: A hypothesis. *Immunobiology* **221**, 116–127 (2016).
15. Arend, P. Early ovariectomy reveals the germline encoding of natural anti-A- and Tn-cross-reactive immunoglobulin M (IgM) arising from developmental O -GalNAc glycosylations. (Germline-encoded natural anti-A/Tn cross-reactive IgM). *Cancer Med.* **6**, 1601–1613 (2017).
16. Qin, H. *et al.* Proteomics Analysis of O-GalNAc Glycosylation in Human Serum by an Integrated Strategy. *Anal. Chem.* **89**, 1469–1476 (2017).
17. Wang, H., Coligan, J. E. & Morse, H. C. Emerging functions of natural IgM and its Fc receptor FcμR in immune homeostasis. *Frontiers in Immunology* **7**, (2016).
18. Willis JR1, Briney BS, DeLuca SL, Crowe JE Jr, M. J. Human Germline Antibody Gene Segments Encode Polyspecific Antibodies. *PLoS Comput. Biol.* (2013). doi:10.1371/journal.pcbi.1003045
19. Armstrong, P. B. & Quigley, J. P. Alpha2-macroglobulin: an evolutionarily conserved arm of the innate immune system. *Dev. Comp. Immunol.* **23**, 375–390 (1999).
20. Stevenson, L. *et al.* α2-Macroglobulin Can Crosslink Multiple Plasmodium falciparum Erythrocyte Membrane Protein 1 (PfEMP1) Molecules and May Facilitate Adhesion of Parasitized Erythrocytes. *PLOS Pathog.* **11**, e1005022 (2015).
21. Matsui, T., Fujimura, Y, Nishida, S. & Titani, K. Human plasma alpha 2-macroglobulin and von Willebrand factor possess covalently linked ABO(H) blood group antigens in subjects with corresponding ABO phenotype. *Blood* **82**, 663–668 (1993).
22. Matsui, T., Hamako, J., Ozeki, Y. & Titani, K. Comparative study of blood group-recognizing lectins toward ABO blood group antigens on neoglycoproteins, glycoproteins and complex-type oligosaccharides. *Biochim. Biophys. Acta - Gen. Subj.* **1525**, 50–57

- (2001).
23. Hofmann, B. T. *et al.* ABO Blood Group IgM isoagglutinins interact with tumor-associated O-glycan structures in pancreatic cancer. *Clin. Cancer Res.* **20**, 6117–6126 (2014).
 24. Sun, W. *et al.* ABO blood types and cancer risk-A cohort study of 339,432 subjects in Taiwan. *Cancer Epidemiol.* **39**, 150–156 (2015).
 25. Vasan, S. K. *et al.* ABO blood group and risk of cancer: A register-based cohort study of 1.6 million blood donors. *Cancer Epidemiol.* **44**, 40–43 (2016).
 26. Nakao, M. *et al.* ABO Genotype and the Risk of Gastric Cancer, Atrophic Gastritis, and Helicobacter pylori Infection. *Cancer Epidemiol. Biomarkers Prev.* **20**, 1665–1672 (2011).
 27. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, S.-S. R. Pancreatic cancer risk and ABO blood group alleles: Results from the Pancreatic Cancer Cohort Consortium. *Cancer Res.* **70**, 1015–1023 (2010).
 28. Hsiao, L., Liu, N., You, S. & Hwang, L. ABO blood group and the risk of cancer among middle-aged people in Taiwan. *Asia Pac J Clin Oncol.* **11**, e31-6 (2015).
 29. Zhang, B., He, N., Huang, Y., Song, F. & Chen, K. ABO blood groups and risk of cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* **15**, 4643–4650 (2014).
 30. Varki, A. & Lowe, J. B. *Chapter 6. Biological Roles of Glycans, Essentials of Glycobiology, 2nd Edition. Essentials of Glycobiology* (2009). at <<http://www.ncbi.nlm.nih.gov/pubmed/20301233>>
 31. Jiang X1, Liu Y1, T. M. Histo-blood group antigens as receptors for rotavirus, new understanding on rotavirus epidemiology and vaccine strategy. *Emerg Microbes Infect.* **6**, e22 (2017).
 32. Gupta, M. & Chowdhuri, A. N. R. Relationship between ABO blood groups and malaria. *Bull. World Health Organ.* **58**, 913–915 (1980).
 33. Mohandas, N. & Narla, A. Blood group antigens in health and disease. *Curr Opin Hematol* **12**, 135–140 (2005).

34. Horuk, R. The Duffy Antigen Receptor for Chemokines DARC/ACKR1. *Front. Immunol.* **6**, 1–3 (2015).
35. Dean, L. in *The ABO blood group* (ed. Copy editor Belinda Beck; Graphic Design: Todd Groesbeck.) Chapter 5 (National Center for Biotechnology Information (NCBI), National Library of Medicine, National Institutes of Health, Bethesda, MD 20892-6510, 2005). doi:10.1160/TH04-04-0251
36. Howes, R. E. *et al.* The global distribution of the Duffy blood group. *Nat. Commun.* **2**, 266 (2011).
37. Rowe, J. A., Opi, D. H. & Williams, T. N. Blood groups and malaria: fresh insights into pathogenesis and identification of targets for intervention. *Curr. Opin. Hematol.* **16**, 480–7 (2009).
38. Panda, A. K. *et al.* Association of ABO blood group with severe falciparum malaria in adults: case control study and meta-analysis. *Malar. J.* **10**, 309 (2011).
39. Shen H, Schuster R, Stringer KF, Waltz SE, L. A. The Duffy antigen/receptor for chemokines (DARC) regulates prostate tumor growth. *FASEB J.* **20**, 59–64 (2006).
40. Liu, X.-F., Li, L.-F., Ou, Z.-L., Shen, R. & Shao, Z.-M. Correlation between Duffy blood group phenotype and breast cancer incidence. *BMC Cancer* **12**, 374 (2012).
41. Maeda, S. *et al.* Duffy antigen receptor for chemokines (DARC) expressing in cancer cells inhibits tumor progression by suppressing CXCR2 signaling in human pancreatic ductal adenocarcinoma. *Cytokine* **95**, 12–21 (2017).
42. Faso, B. *et al.* Different response to Plasmodium falciparum malaria in West African sympatric ethnic groups. *Med. Sci.* **93**, 13206–13211 (1996).
43. Snow, R. W., Guerra, C. A., Noor, A. M., Myint, H. Y. & Hay, S. I. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* **434**, 214–217 (2005).
44. Tekeste, Z. & Petros, B. The ABO blood group and Plasmodium falciparum malaria in Awash, Metehara and Ziway areas, Ethiopia. *Malar. J.* **9**, 280 (2010).
45. Autino, B., Corbett, Y., Castelli, F. & Taramelli, D. Pathogenesis of malaria in tissues and

- blood. *Mediterranean Journal of Hematology and Infectious Diseases* **4**, (2012).
46. Semblat, J. P. *et al.* Identification of the minimal binding region of a Plasmodium falciparum IgM binding PfEMP1 domain. *Mol. Biochem. Parasitol.* **201**, 76–82 (2015).
 47. Rowe, J. A. *et al.* Blood group O protects against severe Plasmodium falciparum malaria through the mechanism of reduced rosetting. *Proc. Natl. Acad. Sci.* **104**, 17471–17476 (2007).
 48. Nagai, M., Davè, V., Kaplan, B. & Yoshida, A. Human blood group glycosyltransferases. I. Purification of n-acetylgalactosaminyltransferase. *J. Biol. Chem.* **253**, 377–9 (1978).
 49. Kreisman, L. S. C. & Cobb, B. A. Infection, inflammation and host carbohydrates: A Glyco-Evasion Hypothesis. *Glycobiology* **22**, 1019–1030 (2012).
 50. Zhang, L. & Ten Hagen, K. G. The cellular microenvironment and cell adhesion: a role for O-glycosylation. *Biochem. Soc. Trans.* **39**, 378–82 (2011).
 51. Ejigiri, I. *et al.* Shedding of TRAP by a rhomboid protease from the malaria sporozoite surface is essential for gliding motility and sporozoite infectivity. *PLoS Pathog.* **8**, 7 (2012).
 52. Arisue, N. *et al.* Clues to evolution of the SERA multigene family in 18 Plasmodium species. *PLoS One* **6**, (2011).
 53. Bourgon, R. *et al.* The serine repeat antigen (SERA) gene family phylogeny in plasmodium: The impact of GC content and reconciliation of gene and species trees. *Mol. Biol. Evol.* **21**, 2161–2171 (2004).
 54. Huang, X. *et al.* The Role of Serine-Type Serine Repeat Antigen in Plasmodium yoelii Blood Stage Development. *PLoS One* **8**, (2013).
 55. Aoki, S. *et al.* Serine repeat antigen (SERA5) is predominantly expressed among the SERA multigene family of Plasmodium falciparum, and the acquired antibody titers correlate with serum inhibition of the parasite growth. *J. Biol. Chem.* **277**, 47533–47540 (2002).
 56. Stallmach, R. *et al.* Plasmodium falciparum SERA5 plays a non-enzymatic role in the malarial asexual blood-stage lifecycle. *Mol. Microbiol.* **96**, 368–387 (2015).

57. Collins, C. R., Hackett, F., Atid, J., Tan, M. S. Y. & Blackman, M. J. The Plasmodium falciparum pseudoprotease SERA5 regulates the kinetics and efficiency of malaria parasite egress from host erythrocytes. *PLoS Pathog.* **13**, e1006453 (2017).
58. Vigan-Womas, I. *et al.* Structural basis for the ABO blood-group dependence of plasmodium falciparum rosetting. *PLoS Pathog.* **8**, 33 (2012).
59. Pantaleo A, Ferru E, Carta F, Mannu F, Giribaldi G, Vono R, Lepedda AJ, Pippia P, T. F. Analysis of changes in tyrosine and serine phosphorylation of red cell membrane proteins induced by P. falciparum growth. *Proteomics* **10**, 3469–79 (2010).
60. Goel, S. *et al.* RIFINs are adhesins implicated in severe Plasmodium falciparum malaria. *Nat. Med.* **21**, 314–317 (2015).
61. Yam, X. Y., Niang, M., Madnani, K. G. & Preiser, P. R. Three Is a Crowd – New Insights into Rosetting in Plasmodium falciparum. *Trends in Parasitology* **33**, 309–320 (2017).
62. Rowe, J. A., Shafi, J., Kai, O. K., Marsh, K. & Raza, A. Nonimmune IgM but not IgG binds to the surface of Plasmodium falciparum-infected erythrocytes and correlates with rosetting and severe malaria. *Am. J. Trop. Med. Hyg.* **66**, 692–699 (2002).
63. Gowda, D. . & Davidson, E. . Protein Glycosylation in the Malaria Parasite. *Parasitol. Today* **15**, 147–152 (1999).
64. Dieckmann ??? Schuppert A, Bender S, Odenthal ??? Schnittler M, Bause E, S. R. *et al.* Apparent lack of N???glycosylation in the asexual intraerythrocytic stage of Plasmodium falciparum. *Eur. J. Biochem.* **205**, 815–825 (1992).
65. Moll, K., Palmkvist, M., Ch'ng, J., Kiwuwa, M. S. & Wahlgren, M. Evasion of immunity to Plasmodium falciparum: Rosettes of blood group a impair recognition of PfEMP1. *PLoS One* **10**, (2015).
66. Kun, J. F. J. J. *et al.* A putative Plasmodium falciparum exported serine/threonine protein kinase. *Mol. Biochem. Parasitol.* **85**, 41–51 (1997).
67. Maenpuen, S., Sopitthummakhun, K., Yuthavong, Y., Chaiyen, P. & Leartsakulpanich, U. Characterization of Plasmodium falciparum serine hydroxymethyltransferase-A potential antimalarial target. *Mol. Biochem. Parasitol.* **168**, 63–73 (2009).

68. Kraatz HB, Martic, S. *Kinomics: Approaches and Applications*. (Wiley-VCH 978-3-527-33765-1, 2015).
69. Bzik, D.J., Li, W.B., Horii, T. and Inselburg, J. Amino acid sequence of the serine-repeat antigen (SERA) of *Plasmodium falciparum* determined from cloned cDNA. *Mol. Biochem. Parasitol.* **30**, 279–288 (1988).
70. Yazer, M.H., Hosseini-Maaf, B. & Olsson, M. L. Blood grouping discrepancies between ABO genotype and phenotype caused by O alleles. *Curr. Opin. Hematol.* **15**, 618–624 (2008).
71. O’Keefe, D. S. & Dobrovic, A. A rapid and reliable PCR method for genotyping the ABO blood group. II: A2 and O2 alleles. *Hum Mutat* **8**, 358–361 (1996).
72. Seltsam, A., Hallensleben, M., Kollmann, A. & Blasczyk, R. Nondeletional ABO*O alleles express weak blood group A phenotypes. *Transfusion* **45**, 359–365 (2005).
73. Salanti, A. *et al.* Targeting Human Cancer by a Glycosaminoglycan Binding Malaria Protein. *Cancer Cell* **28**, 500–514 (2015).
74. Lo, E. *et al.* Molecular epidemiology of *Plasmodium vivax* and *Plasmodium falciparum* malaria among Duffy-positive and Duffy-negative populations in Ethiopia. *Malar. J.* **14**, 84 (2015).
75. Qin, L. *et al.* Worldwide malaria incidence and cancer mortality are inversely associated. *Infect. Agent. Cancer* **12**, (2017).
76. Reynaldi, A. *et al.* Impact of *Plasmodium falciparum* Coinfection on Longitudinal Epstein-Barr Virus Kinetics in Kenyan Children. *J. Infect. Dis.* **213**, 985–991 (2016).
77. Chene, A. *et al.* Endemic Burkitt’s lymphoma as a polymicrobial disease. New insights on the interaction between *Plasmodium falciparum* and Epstein-Barr virus. *Seminars in Cancer Biology* **19**, 411–420 (2009).
78. Silva-Gomes, S., Decout, A. & Nigou, J. in *Encyclopedia of Inflammatory Diseases* 1–16 (2015). doi:10.1007/978-3-0348-0620-6_35-1
79. Takeuchi, O. & Akira, S. Pattern Recognition Receptors and Inflammation. *Cell* **140**, 805–820 (2010).

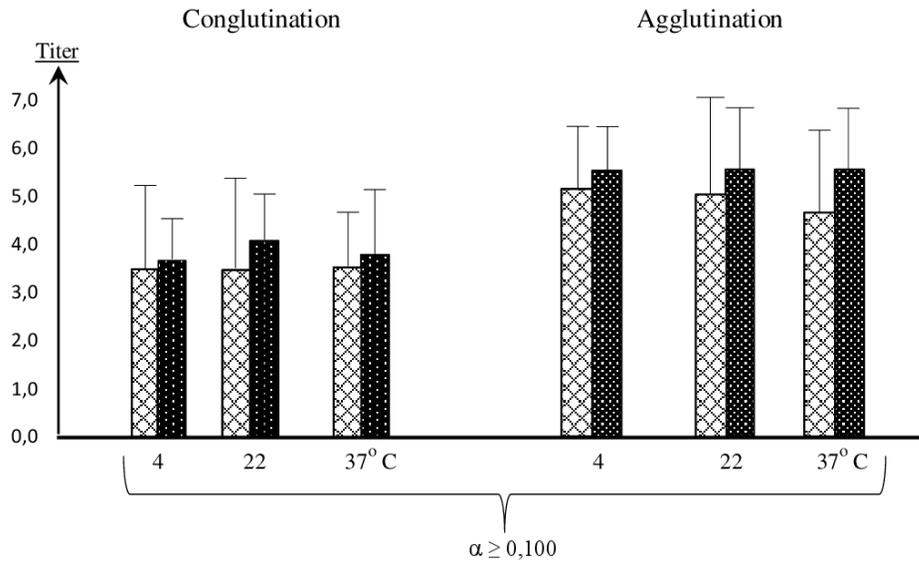
80. Saitou, N. & Yamamoto, F. Evolution of primate ABO blood group genes and their homologous genes. *Mol. Biol. Evol.* **14**, 399–411 (1997).
81. Hakomori, S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. *Biochim Biophys Acta.* **1473**, 247–66 (1999).
82. Ségurel, L. *et al.* The ABO blood group is a trans-species polymorphism in primates. *Proc. Natl. Acad. Sci. U. S. A.* **109**, 18493–8 (2012).
83. Arend, P. An auto-reactive A-like ovarian determinant distinct from xeno-reactive A-like structures. *Immunobiology* **156**, 410–7. (1980).
84. Pickard, J. M. & Chervonsky, A. V. Intestinal Fucose as a Mediator of Host–Microbe Symbiosis. *J. Immunol.* **194**, 5588–5593 (2015).
85. Petersen, A. M. & Krogfelt, K. A. Helicobacter pylori: An invading microorganism? A review. in *FEMS Immunology and Medical Microbiology* **36**, 117–126 (2003).
86. Harris, J. B. *et al.* Blood group, immunity, and risk of infection with Vibrio cholerae in an area of endemicity. *Infect. Immun.* **73**, 7422–7427 (2005).
87. Harris, J. B. & LaRocque, R. C. Cholera and ABO Blood Group: Understanding an Ancient Association. *Am. J. Trop. Med. Hyg.* **95**, 263–264 (2016).
88. Chmiela, M., Miszczyk, E. & Rudnicka, K. Structural modifications of Helicobacter pylori lipopolysaccharide: An idea for how to live in peace. *World Journal of Gastroenterology* 9882–9897 (2014). doi:10.3748/wjg.v20.i29.9882
89. Huang, Y., Wang, Q.-L., Cheng, D.-D., Xu, W.-T. & Lu, N.-H. Adhesion and Invasion of Gastric Mucosa Epithelial Cells by Helicobacter pylori. *Front. Cell. Infect. Microbiol.* **6**, 159 (2016).
90. Burnet FM and Stone JD. The receptor-destroying enzyme of V. cholerae. *Aust J Exp Biol Med Sci.* **25**, 227–33 (1947).
91. Jones, G. W. & Freter, R. Adhesive properties of Vibrio cholerae: nature of the interaction with isolated rabbit brush border membranes and human erythrocytes. *Infect. Immun.* **14**, 240–245 (1976).
92. Klein P. Newman R. Müller P. Uhlenbruck G. Schaefer H. Lennartz Fischer R.

- Histochemical methods for the demonstration of thomsen-friedenreich antigen in cell suspensions and tissue sections. *Klinische Wochenschrift* **56**, 761–765 (1978).
93. Reepmaker, J. The Relation Between Polyagglutinability of Erythrocytes in vivo and the Hübener-Thomsen-Friedenreich Phenomenon. *J Clin Pathol.* **5**, 277–270 (1952).
 94. Yamamoto, T., Kamano, T., Uchimura, M., Iwanaga, M. & Yokota, T. Vibrio cholerae O1 adherence to villi and lymphoid follicle epithelium: In vitro model using formalin-treated human small intestine and correlation between adherence and cell-associated hemagglutinin levels. *Infect. Immun.* **56**, 3241–3250 (1988).
 95. Yamamoto, T. & Yokota, T. Adherence targets of Vibrio parahaemolyticus in human small intestines. *Infect. Immun.* **57**, 2410–2419 (1989).
 96. Bhende Y., Desphande C., Bhatia H., Sanger R, Race R., Morgan W. & Watkins, W. A “new” blood group character related to the ABO system. *Lancet* **1**, 903–4. (1952).
 97. Arend, P. *ABO phenotype protected reproduction based on specific fucosylations and explained by Bombay type formation.* (2017). doi:10.6084/m9.figshare.1409398.v404
 98. Echenberg, M. J. *Africa in the time of cholera: a history of pandemics from 1815 to the present.* *African studies* (2011). doi:10.3201/eid1802.111535
 99. Mutreja, A. *et al.* Evidence for several waves of global transmission in the seventh cholera pandemic. *Nature* **477**, 462–465 (2011).
 100. Chowdhury, F. R., Nur, Z., Hassan, N., von Seidlein, L. & Dunachie, S. Pandemics, pathogenicity and changing molecular epidemiology of cholera in the era of global warming. *Ann Clin Microbiol Antimicrob* **16**, 10 (2017).
 101. Dean, L. Blood Groups and Red Cell Antigens. *Blood Groups Red Cell Antigens* (2005). doi:10.1160/TH04-04-0251
 102. Payne, M. J., Campbell, S., Patchett, R. A. & Kroll, R. G. The use of immobilized lectins in the separation of Staphylococcus aureus, Escherichia coli, Listeria and Salmonella spp. from pure cultures and foods. *J. Appl. Bacteriol.* **73**, 41–52 (1992).
 103. Friedenreich, V. & Munck, J. Intravital Effects of „Transformed” Blood Corpuscles in Guinea-Pigs. *Acta Pathol. Microbiol. Scand.* **7**, 134–145 (1930).

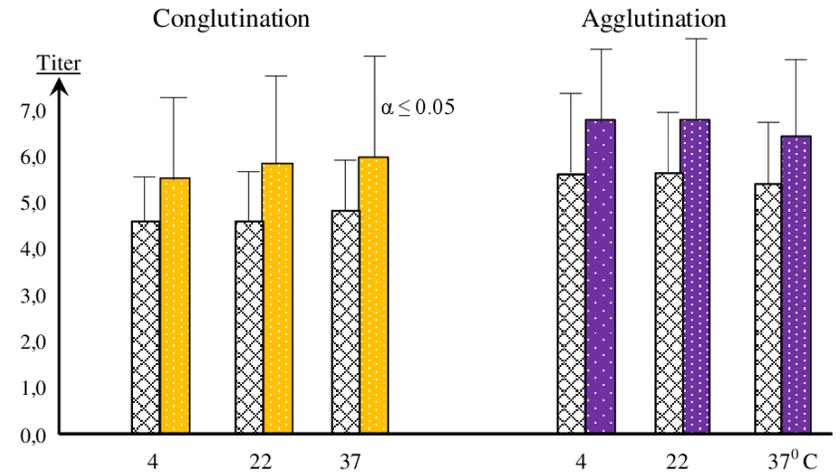
104. Moreau R, Dausset J, Bernard J, M. J. Acquired hemolytic anemia with polyagglutinability of erythrocytes by a new factor present in normal blood (Article in French). *Bull Mem Soc Med Hop Paris*. **73**, 569–87 (1957).
105. Taus, C. *et al.* Expression and characterization of the first snail-derived UDP-N-acetyl-(alpha)-D-galactosamine: Polypeptide N-acetylgalactosaminyltransferase. *Glycoconj. J.* **30**, 354 (2013).
106. Staudacher, E. Mucin-Type O-Glycosylation in Invertebrates. *Molecules* **20**, 10622–10640 (2015).
107. Sanchez, J. F. *et al.* Biochemical and structural analysis of *Helix pomatia* agglutinin: A hexameric lectin with a novel fold. *J. Biol. Chem.* **281**, 20171–20180 (2006).
108. Hammarström, S. Binding of *Helix Pomatia* A Hemagglutinin to Human Erythrocytes and their Cells. Influence of Multivalent Interaction on Affinity. *Scand. J. Immunol.* **2**, 53–66 (1973).
109. Domino, S., Zhang, L., Gillespie, P., Saunders, T. & Lowe, J. Deficiency of reproductive tract alpha(1,2)fucosylated glycans and normal fertility in mice with targeted deletions of the FUT1 or FUT2 alpha(1,2)fucosyltransferase locus. *Mol. Cell. Biol.* **21**, 8336–45 (2001).
110. Dupuy, F., Germot, A., Marena, M., Oriol, R., Blancher, A., Julien, R. & Maftah, A. Alpha1,4-fucosyltransferase activity: a significant function in the primate lineage has appeared twice independently. *Mol. Biol. Evol.* **19**, 815–24 (2002).
111. Apoil P., Roubinet, F., Despiau, S., Mollicone, R., Oriol, R. & Blancher, A. Evolution of alpha 2-fucosyltransferase genes in primates: relation between an intronic Alu-Y element and red cell expression of ABH antigens. *Mol Biol Evol.* **17**, 337–51 (2000).

Selective immune response of blood group O individuals to increased enteral absorption

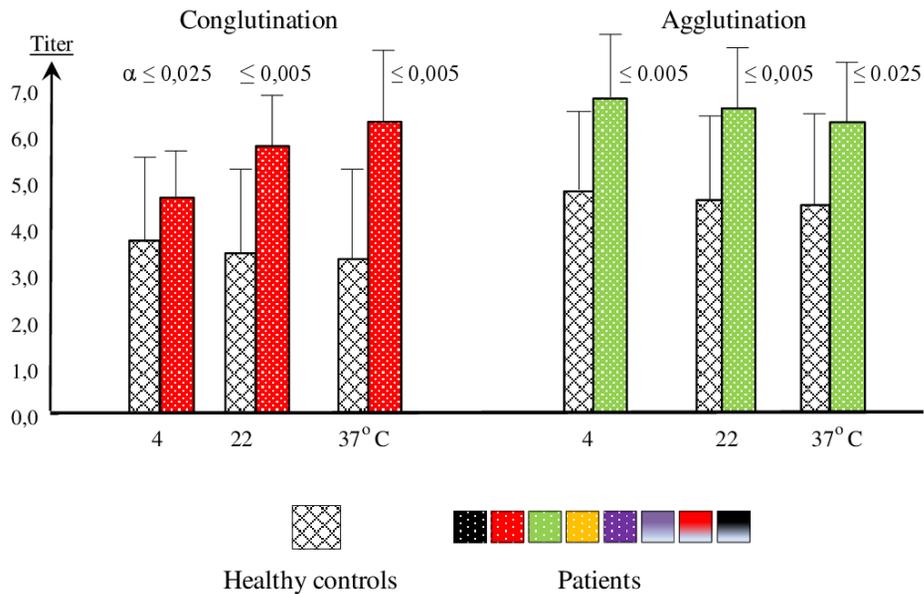
Anti-B blood group A



Anti-A blood group O



Anti-B blood group O



Conglutination÷Agglutination

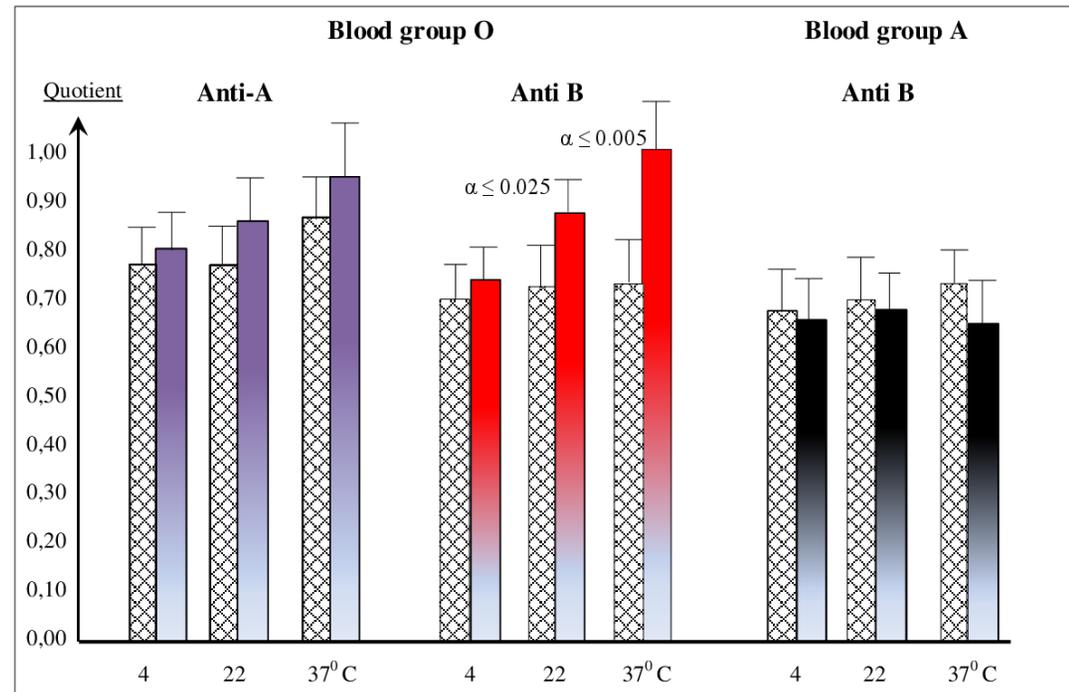


Fig. 1

Fig. 1. Spontaneous variations in the production of anti-A/B isoagglutinins in 21 individuals suffering from ulcerative colitis (blood group A = 11, blood group O = 10), and in 42 normal persons (blood group A = 22, blood group O = 20). The grade of immunization and dominance of the 7S (IgG) congrutinating and 19S (IgM) agglutinating immunoglobulins were determined by measuring congrutinin and agglutinin titer and their quotients at three different temperatures. Using the non-parametric *Wilcoxon* procedure, the anti-B-reactive IgG and IgM levels in blood group A plasma remained within normal range, whereas the blood group O patients exhibited the statistically significant stimulation of an IgG congrutinating and IgM agglutinating anti-B response as well as an asymmetrically cross-reactive, less pronounced anti-A specific IgG response, and the IgG/IgM quotients indicate the predominance of the IgG class. The figure is reconstructed from the data published in: Arend & Fehlhaber (1969).⁶

*Molecular mechanisms of infectious diseases
- phenotypic accommodation of the pathogen*

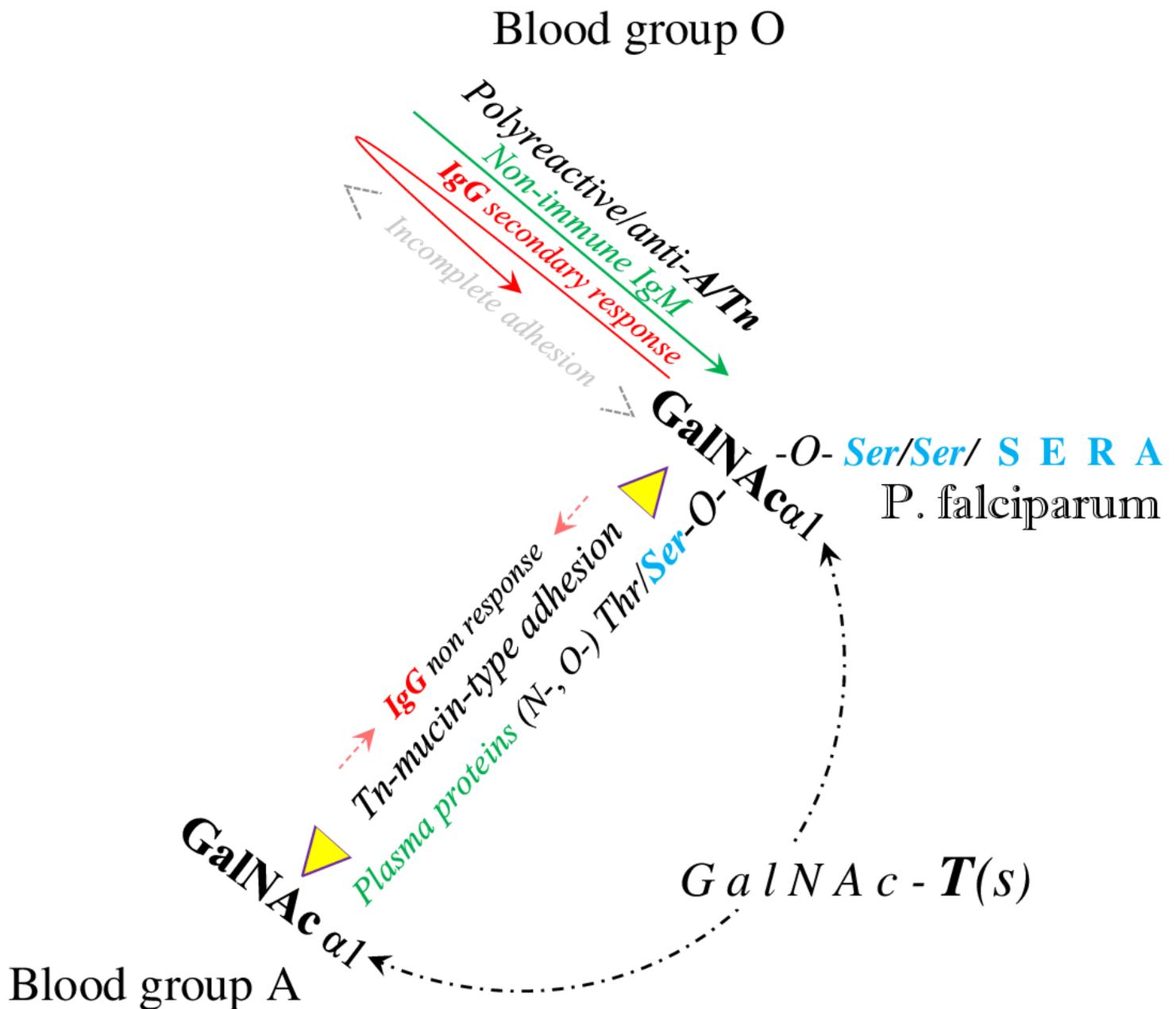


Fig. 2

Fig. 2. Complementarity and adhesion of mammalian structures to a pathogen exclude the formation of adaptive and innate antibody reactivity against the resulting hybrid antigen. The parasite *Plasmodium falciparum* exhibits molecular complementarity to blood A synthesis by serine repeat antigen (SERA), exerting a surplus of serine residues, which may function as acceptor sites on the surface of inoculated sporozoites for soluble blood group A-determining plasma transferase, α 1-3-N-GalNAc-T, hypothetically synthesizing a trans-species, hybrid A-like, Tn-mucin-type GalNAc-1-O-Ser/Thr-R structure. Blood group A cannot respond by immunoglobulin G (IgG) antibodies to A or A-like cross-reactive Tn structures due to clonal selection, while the non-immune IgM undergoes phenotypic accommodation, moreover, gets involved in the adhesion mechanism by its Fc-region⁶² via O-GalNAc glycosylation of germline-serine-residues¹⁸. Individuals with blood group O(H) lacking this enzyme, may not develop this hybrid antigen and maintain the antibodies against it, while the parasite does not completely get attached to the cell membranes of the host.

Central immunological position of the
human histo (blood) group O(H)

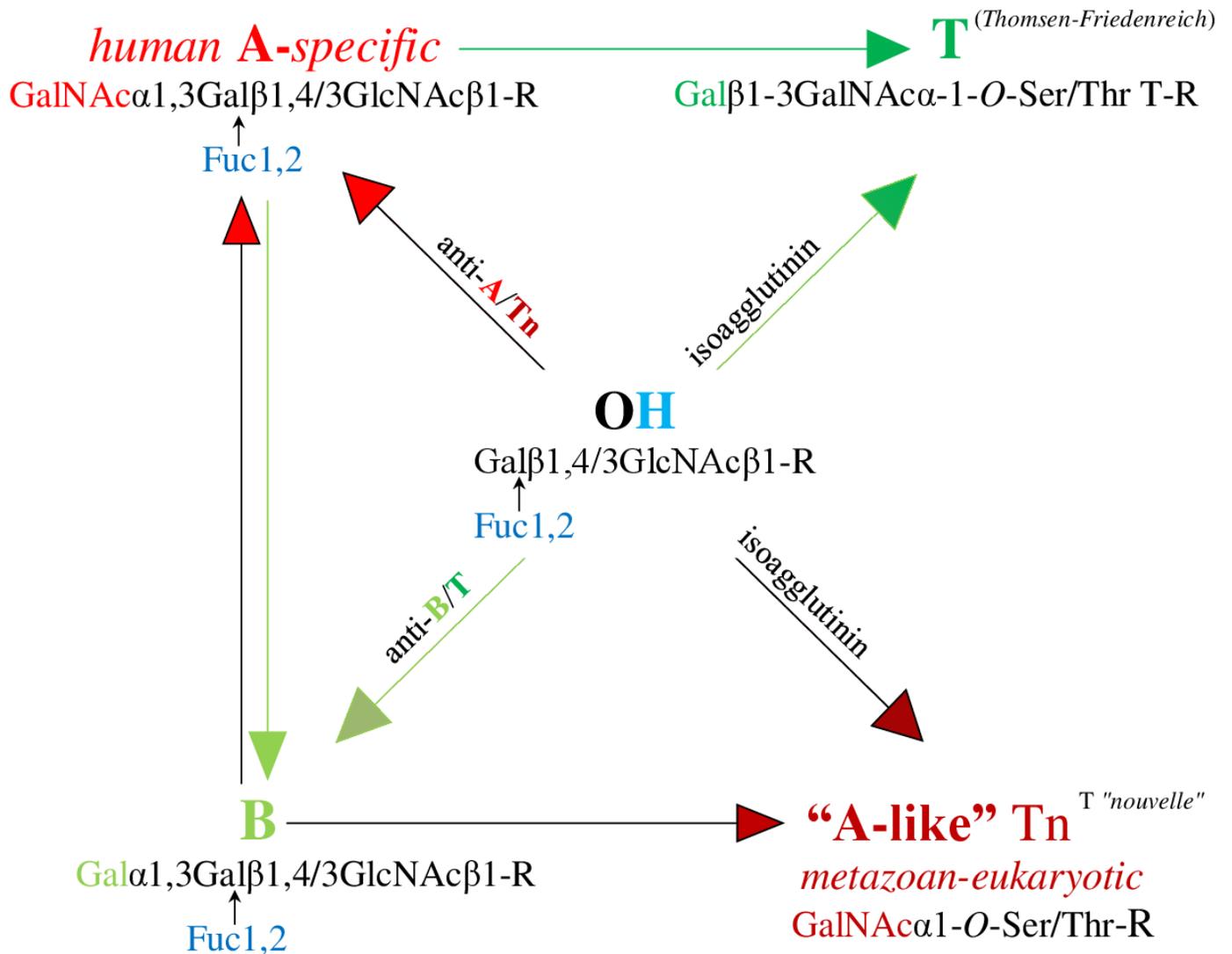


Figure 3.

Fig. 3. The central immunological position of blood group O(H) is evident based on its comprehensive presentation of both adaptive and germline-encoded “natural” antibodies against all mature A and B glycans and their cross-reactive developmental structures Tn and T. Human A-specific (A-allelic) glycosylation and trans-species “A-like” Tn formation are developmentally connected via the formation of cross-reactive anti-A/Tn isoagglutinin. According to Hofmann et al.(2014)²³, 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 an anti-Tn antibody that does not react with blood group B red cells or T glycoconjugates. By contrast, the anti-B antibodies of blood group A sera and blood group O(H) sera bind to B and T glycoconjugates but not to A or Tn glycoconjugates. This was figure constructed by Arend (2017).¹⁵