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ABO in the Context of Blood Transfusion and Beyond

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1. Introduction

ABO histo-blood group system is widely acknowledged as one of the antigenic systems most relevant to blood transfusion, but also cells, tissues and organs transplantation. This chapter will illustrate a series of subjects related to blood transfusion but will also give an overview of ABO related topics such as its genetics, biochemistry and its association to human disease as well as a historical section. We decided not to include much detail about the related Lewis oligosaccharide antigens which have been reviewed extensively elsewhere (Soejima & Koda 2005) in order to focus on ABO and allow the inclusion of novel and exciting developments.

ABO group	A/B antigens on red blood cells	Anti-A/-B in serum	Genotype
O	None	Anti-A and Anti-B	O/O
A	A	Anti-B	A/A or A/O
B	B	Anti-A	B/B or B/O
AB	A and B	None	A/B

Table 1. Simple classification of ABO phenotypes and their corresponding genotypes.

As its simplest, the ABO system is dictated by a polymorphic gene (ABO) whose different alleles encode for a glycosyltransferase (A or B) that adds a monosaccharide (N-acetyl-D-galactosamine or D-galactose, respectively) to a specific glycan chain, except for the protein O which is not active. The 3 main alleles: A, B and O are inherited in a classical codominant Mendelian fashion (with O being recessive) and produce, when a pair of them are combined in a diploid cell, the very well known four phenotypic groups (see Table 1). Being one of the first known and easily detectable polymorphic traits in humans, it has been extensively studied as a historical background illustrates.

2. History

Various advancements in both blood storage and serology have contributed to the development of safe blood transfusion. One of the key events that brought transfusion

medicine forward was the discovery of the ABO blood group system. The first successful attempts of human to human blood transfusion already started in the 18th century, but it was an unsafe process in which some patients died. It was not until 1900 when the Austrian pathologist, Karl Landsteiner discovered the ABO blood group system, which opened the door for performing safe blood transfusions (Landsteiner, 1900).

Landsteiner separated the cell components and the sera of blood samples from different individuals, including his own blood, and mixed them in various combinations. He observed that in some combinations red blood cells (RBCs) agglutinated. According to these agglutination patterns, Landsteiner classified the individuals in three different groups. These blood groups were called A, B and C (later called the blood group O). One year later, Decastello and Sturli described one new group, the AB blood group (von Decastello & Sturli, 1902).

Landsteiner theorized that the RBCs possessed two different markers (antigens A and B) able to react with the corresponding sera antibodies (anti-A and anti-B), and as opposite to many other blood group systems such as the Rh system, the presence of the antibodies against A or B occurs naturally in individuals that do not express the antigens. The serum from an individual with A type RBCs present antibodies against the B antigen, so it is able to agglutinate B and AB type RBCs, but not his own type. The serum from B type individuals agglutinates A and AB type RBCs. Finally, the serum from O group can agglutinate A, B and AB RBCs because it contains both anti-A and anti-B antibodies while the serum of AB group do not have reactivity towards none of these antigens. This phenomenon was later known as Landsteiner's Law.

From that first discovery of the ABO system, new developments took place relatively fast during the following years. On 1908, Epstein and Ottenberg suggested that the blood groups could be an inherited character (Epstein & Ottenberg, 1908). That was confirmed in 1910 by von Dungern and Hirszfeld who showed that inheritance of the A and B antigens obeyed Mendel's laws (von Dungern & Hirszfeld, 1910). In fact, ABO was one of the first genetic markers to be used in paternity testing and forensic medicine.

To explain the mode of inheritance, Berstein proposed, in 1924, the one gene locus-three alleles model. He assumed that the A, B and O genes were alleles at the same ABO genetic locus and that the A and B alleles were co-dominant against the recessive O allele (Crow, 1993).

Already by 1926, it was shown that A and B antigens were not restricted to the surface of erythrocytes. They were also found in semen and saliva, and four years later, Putkonen and Lehrs discovered that the ability to secrete these antigens was genetically independent from the ABO gene and inheritable in a classical dominant Mendelian manner (Putkonen, 1930).

In 1950s, two research groups, one led by Kabat and another group led by Watkins and Morgan elucidated the chemical nature of ABH substances (H antigens were found abundantly in individuals with blood group type O) (Kabat, 1956; Morgan, 1960; Watkins, 1981). They determined that they were oligosaccharide antigens and also pointed out the biochemical difference between A (with a terminal N-acetylgalactosamine) and B (with galactose instead) substances. Moreover, they demonstrated that the ABO blood group system antigens were not the primary gene products (i. e. protein antigens), but were the result of enzymatic reactions producing carbohydrate chains. In the following years various works established the tissue distribution of these antigens and their changes during embryonic development (Ravn & Dabelsteen, 2000).

Between 1970 and 1980, the metabolic pathways leading to the biosynthesis of ABH antigens were established (Watkins, 1981) and in 1976, the ABO locus was localized and assigned to chromosome 9q34 (Ferguson-Smith et al., 1976).

In 1990, after the purification of the soluble form of human A transferase by Clausen and collaborators (Clausen et al., 1990), Yamamoto and his group were able to clone the cDNAs for A glycosyltransferase first (Yamamoto et al., 1990b) and afterwards those for the B glycosyltransferase and the O protein and elucidated the molecular basis for the synthesis of A and B antigens (Yamamoto et al., 1990a). Since the original description of the main alleles (A1, B, O) many others have been described by them and other groups and they have been annotated and included in public databases.

Together with the amino acid substitutions between A and B transferases, as well as the mutations causing a decrease or ablation of the enzymatic activity in A/B weak subgroup alleles and O alleles, the determination of their 3-D structure has facilitated a better understanding of the structure-functional relationship of these transferases (Patenaude et al., 2002).

3. Biochemistry and structure

A and B antigens share the same structure except for a terminal sugar bound by an α1-3 glycosidic linkage to galactose (see Fig. 1). In the case of A antigen the last sugar is N-acetylgalactosamine (GalNAc) while in the case of B antigen the last sugar is galactose (Gal).

If these two terminal sugars are eliminated from the common structure the corresponding antibodies lose their reactivity. Therefore these sugars are immunodominant within the epitope. The H antigen is the natural precursor of A and B antigen and its fucose residue is required for A and B glycosyltransferases to recognize it as the acceptor and transfer GalNAc or Gal to its terminal Gal. In the case of O individuals it rests without further elongation.

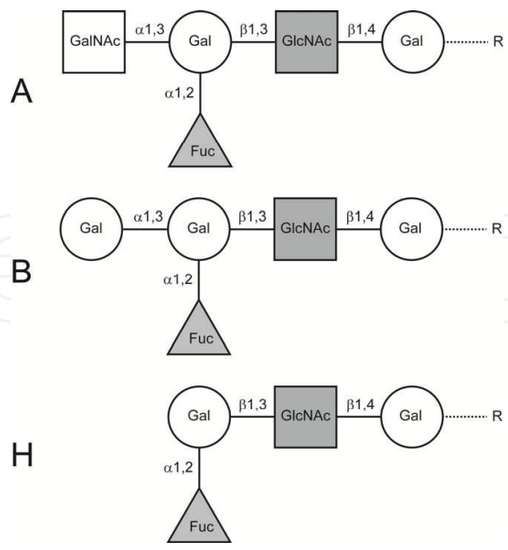

Fig. 1. ABH antigens of Type 2 core structure are schematically drawn showing their chemical composition and the nature of their glycosidic bonds. GalNAc, Gal, GlcNAc and Fuc stand for N-acetylgalactosamine, galactose, N-acetylglucosamine and fucose respectively. R represents the reducing end of the carbohydrate chain.

These antigens reside at the end of carbohydrate structures of variable length. Depending on the disaccharide precursor core chain on which ABH determinants are synthesized, they can be further divided into different types:

Type 1: Galβ1->3GlcNAcβ1-> R

Type 2: Galβ1->4GlcNAcβ1-> R

Type 3: Galβ1->3GalNAcα1-> R

Type 4: Galβ1->3GalNAcβ1-> R

Type 5: Galβ1->3Galβ1-> R

Type 6: Galβ1->4Glcβ1-> R

The internal reducing end of these precursors is bound to carrier molecules (R) of diverse nature: oligosaccharides, glycolipids or glycoproteins (Clausen & Hakomori, 1989). Types 1 through 4 are found on RBCs although Type 2 is the most common on those cells, while Type 6 is present in free oligosaccharides and some tissues (renal vein, intestinal cells) (Björk et al., 1987; Holgersson et al., 1990). Finally Type 5 is synthetic and it was utilized in the characterization of monoclonal antibodies against ABH (Oriol et al., 1990). In turn, these antigens can be present on the cell membrane bound to embedded glycoproteins or glycolipids or also forming part of these glycoconjugates but suspended in fluids as plasma or exocrine secretions and finally as free oligosaccharides without any protein or lipid carrier.

3.1 Carrier molecules

ABH substances are present on glycoproteins as terminal structures of two main types of protein modifying glycans: N-glycans and O-glycans. N-glycans are highly branched oligosaccharides attached to the amide nitrogen of asparagine through an N-acetylglucosamine residue while O-glycans, which could be simple or complex structures, are attached to the hydroxyl oxygen atom of serine or threonine residues through N-acetylgalactosamine sugar.

On RBCs, ABH antigens are present as terminal modifications of N-glycans. The most abundant glycoproteins carrying these ABH determinants are the anion exchange protein band 3, and the glucose transport protein band 4.5, as well as the urea transporter and the water channel AQP1 (aquaporin-1), which are the carrier of blood groups Kidd and Colton, respectively (Fukuda & Fukuda, 1981; Smith et al., 1994; Lucien et al., 2002). The other most abundant red cell glycoprotein, glycophorin A, on which the MNS blood group resides, does not appear to carry any ABH antigen.

Apart from glycoproteins, ABH antigens are also found as terminal modifications of glycolipids. Before 1980, it was generally considered that most of ABH determinants on RBCs were actually carried on glycosphingolipids but after that year several studies demonstrated that glycoproteins were the main carriers (Finne et al., 1980). ABH antigens on lipids are carried predominantly by glycosphingolipids. These molecules consist of a carbohydrate chain attached to ceramide, and according to the nature of the internal carbohydrate chain they are classified into six different series:

Lacto series:	Galβ1->3GlcNAcβ1->3Galβ1->4Glcβ1->Cer
Neolacto series:	Galβ1->4GlcNAcβ1->3Galβ1->4Glcβ1->Cer
Ganglio series:	Galβ1->3GalNAcβ1->4Galβ1->4Glcβ1->Cer
Isoganglio series:	Galβ1->3GalNAcβ1->3Galβ1->4Glcβ1->Cer
Globo series:	GalNAcβ1->3Galα1->4Galβ1->4Glcβ1->Cer
Isoglobo series:	GalNAcβ1->3Galα1->3Galβ1->4Glcβ1->Cer

On each of these structures ABH antigens can be added to the terminal sugar being the most common the Lacto and the Neolacto series.

Additionally, free oligosaccharides containing ABH activity are also found in milk and urine. In this case, these glycans are synthesized mostly from Type 6 precursor chain (Kobata et al., 1978; Lundblad, 1978).

3.2 Antigen distribution

ABH antigens were discovered on RBCs but are also present in many other tissues. For that reason they are also called histo-blood group antigens. In blood, apart from RBCs, platelets also present these antigens although in variable quantities depending on the individuals and their blood group. ABH antigens are detected on endothelial cells and epithelia from the lung and the gastrointestinal tract and also on the lining of the urinary and reproductive tracts. The presence of the antigens is therefore relevant for cell, tissue or organ transplantation (reviewed in (Ravn & Dabelsteen, 2000)).

4. ABO gene and the A and B antigens biosynthesis

We mentioned before that these glycan antigens are not directly encoded by genes. The A and B antigens are synthesized by enzymatic reactions catalyzed by two different enzymes called glycosyltransferases (transferases), the A transferase (α1,3-N-acetyl-D-galactosaminyltransferase) and the B transferase (α1,3-D-galactosyltransferase), respectively. Both, A and B transferases catalyze the last step on the synthesis of A and B antigen adding a GalNAc or a Gal to a precursor chain, the H antigen, by an identical α1-3 glycosidic linkage (for a review in glycosyltransferase biochemistry see (Hakomori, 1981)).

The gene is located in the long arm of chromosome 9 (9q34) and extends over more than 18 kilobases (kb). The gene has the coding sequence distributed in 7 exons, being the last one the largest. The glycosyltransferase catalytic domain is encoded in the last two exons. The 3'UTR region contains repetitive sequences that could be involved in the mRNA stability. Promoter activity resides in the gene sequence just upstream of the transcription initiation site (Yamamoto et al., 1995).

Probing cDNA libraries obtained from human adenocarcinoma cell lines of different ABO phenotypes, we successfully defined the main alleles. It was concluded that the distinct donor nucleotide-sugar specificity between A and B transferases is the result of 7 substitutions out of 1062 coding nucleotides, and only 4 of them resulting in amino acid substitutions (Arginine, Glycine, Leucine and Glycine in A transferase and Glycine, Serine, Methionine and Alanine for B transferase at codons 176, 235, 266, 268) (Yamamoto et al., 1990a).

Together with previous mutagenic studies (Yamamoto & McNeill 1996), the elucidation of the 3-D structure of the glycosyltransferases has allowed to clarify the roles of these amino acids (Patenaude et al., 2002) (see Fig. 2). The amino acid residues at codons 266 and 268 are directly involved in the recognition and binding of the sugar portion of the nucleotide-sugar donor substrates in the glycosyltransferase reaction. The amino acid residue at codon 176 is relatively far from the catalytic center, while the amino acid residue at codon 235 is at a middle distance.

The O allele encodes a non-functional glycosyltransferase enzyme. Most of O alleles contained a single nucleotide deletion at the 261 position, relatively close to the N-terminal of the coding sequence, resulting in a codon frameshift starting from amino acid 88 in the protein sequence, which causes the production of a truncated non-functional protein. This truncated protein has no catalytic domain and its mRNA transcript is less stable (O'Keefe & Dobrovic, 1996).

The antigen biosynthesis realized by the active glycosyltransferases takes place in the Golgi apparatus. These transferases are classified as type II transmembrane proteins as their structures follow the common pattern of a short transmembrane domain followed by a stem region and a catalytic domain within the Golgi lumen. The 3-D structure showed that the catalytic site is composed of two main domains. The N-terminal domain recognizes the nucleotide-sugar donor substrate. In the case of the A allele, which encodes for an α1,3-N-acetylgalactosaminyltransferase, the sugar donor is uridine diphosphate-N-acetyl-D-galactosamine (UDP-GalNAc) while the B gene product, an α1,3-galactosyltransferase transfers galactose from UDP-galactose. The C-terminal domain binds to the acceptor substrate, the fucosylated galactosyl residue of the H antigen.

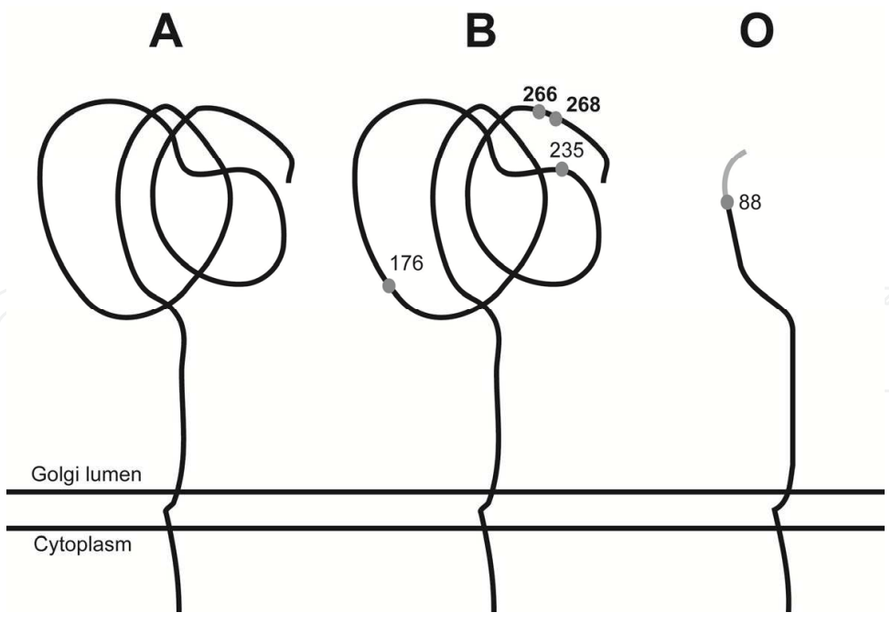

Fig. 2. Schematics with the main alleles' products and their modified residues. The different amino acids are numbered on B, in boldface the ones defining the sugar donor specificity, while in O the first amino acid after the frameshift is indicated and the alternative translation is in grey.

Since the discovery of the major alleles numerous polymorphisms/mutations have been described for the ABO gene (Yamamoto, 2004). The majority of these variations are nucleotide changes resulting in amino acid substitutions or a single nucleotide deletion/insertion and correlate well with the presence of specific subgroup phenotypes. At the moment the total number of alleles deposited in the ABO system section of the Blood Group Antigen Gene Mutation Database (dbRBC at NCBI http://www.ncbi.nlm.nih.gov/gv/mhc/xslcgi.cgi?cmd=bgmut/home) has surpassed 270 and considering the rapid advancement of next-generation sequencing, this number is going to increase in the coming years.

5. Subgroups of A and B

Many weak subgroups have been described for A group and a lower number for B group. These rare phenotypes account for a minority of individuals. Different strategies have been developed to test for these less common occurrences when the results of forward and reverse tests do not match or other inconsistencies are found (genetic for example).

The first subgroups to be recognized were A_1 and A_2. In 1910, Dungern and Hirszfeld noticed differences in the amount of A antigen expression present in A individuals (von Dungern & Hirszfeld, 1910). It was also observed that serum from B group blood presented two different antibodies reacting to A RBCs. One general anti-A that was able to react towards all A erythrocytes, and one specific to A_1. A_1 phenotype is characterized by the presence of a higher number of A antigen when compared to A_2 (Rochant et al., 1976). The A^1 allele is dominant over A^2 and encodes for an A transferase with higher affinity and reactivity for the substrates of the reaction (UDP-GalNAc and H-antigen/2'-fucosyllactose) than the A_2 transferase (Schachter et al., 1973).

Other subgroups of A include weak expressors of the antigen (A_3, A_{end}, A_{finn}, A_{bantu}, A_x, A_m, A_y, A_{el}) and the intermediate phenotype between A_1 and A_2, A_{int}. Cartron developed a method to assess the relative agglutinability of cells by radiolabelled anti-A antibodies. This quantification permitted to classify the phenotypes in respect to RBC A antigen expression and demonstrated substantial individual variation within the subgroups (Cartron et al., 1974). Further characterization includes the determination of anti-A or anti-A_1, the A transferase activity in serum, and the presence of A and/or H antigens in saliva.

The B phenotype does not present so many variants and they are more difficult to cluster in coherent groups so the weak variants have been classified by similarity to A subgroups. They are B_3, B_x, B_m, B_{el} and B_w and present various degrees of B transferase activity in plasma and secretions and weak B antigen expression.

It has to be pointed out that the phenotypic classifications do not completely correlate genetically as different weak alleles may be included in each subgroup and some have not been included in any of the existing categories (polymorphisms reviewed in (Yip, 2002)).

An interesting phenomenon has been reported, which was recognized by not adhering to classic Mendelian type of inheritance. Usually, the expression of A and B antigens is specified by two separate A and B alleles, one derived from the mother and the other one derived from the father. That is known as a common AB phenotype (*trans*-AB). However, in

unusual cases of AB phenotype the expression of both A and B antigens is apparently specified by a single gene derived from either one of the parents resulting in what it is referred to as *cis*-AB (Yamamoto et al., 1993a; Yazer et al., 2006).

A similar phenomenon named B(A) was reported when weak A reactivity was demonstrated using a monoclonal anti-A reagents on the blood of certain B-type individuals. It appears that small quantities of A antigens, in addition to larger quantities of B antigens, were produced by special B transferase. Various different alleles for both *cis*-AB and B(A) have been found (Yamamoto et al., 1993b).

The assignment to these subgroups and its confirmation requires further tests than forward and reverse typing and may include the detection of the transferase activity in serum, the detection of antigens in saliva and/or genetic confirmation.

6. H and Secretor genes and related phenotypes

A and B antigen are synthesized on the same common fucosylated precursor, the H antigen. This precursor is produced by the transfer of an L-fucose residue from guanosine diphosphate (GDP)-L-fucose to the C-2 position of the terminal galactose of Type 1 or 2 core precursor chains using an α1-2 glycosidic bond. There are two α1,2-L-fucosyltransferases that are able to catalyze this reaction, encoded by two genes, FUT1 (H) and FUT2(Se). Both produce H-active structures but their expression is tissue-dependent. On one hand, the Hh system is a blood group on its own and it is closely related to ABO. On the other hand, the product of the Secretor gene allows the ABH antigens to be present in secretions and therefore it is also of relevance. Both genes and the related phenotypes will be discussed briefly.

6.1 Hh

H-transferase, the product of FUT1 is primarily present in tissues derived from ectoderm and mesoderm and is responsible for the synthesis of RBCs, bone marrow, vascular endothelium, skin and primary sensory neurons H antigens.

FUT1 and FUT2 share about 70% sequence identity and are 35 kb apart on the long arm of chromosome 19 (19q13.3). FUT1 gene consists of 4 exons, and the catalytic region is contained in the last one. Only one transcript has been described and it is translated into a 365 amino acid long protein. In addition, FUT1 has a preferential affinity for Type 2 acceptor substrate than for Type 1.

Some FUT1 alleles producing H-deficient phenotypes have been described due to different types of mutations, mostly missense mutations, but also to deletions causing frameshifts in the coding region. Those without or reduced enzymatic activity (h alleles) are the cause of the Bombay and para-Bombay phenotypes. The Bombay phenotype is characterized by the total absence of H antigen on RBCs and secretions irrespectively of the ABO status. These individuals are typed as O by the routine ABO typing because the A or B transferases, even if present, cannot synthesize their products due to the absence of precursor. These phenotypes are very uncommon but can be locally relevant (Mollicone et al., 1995).

6.2 Secretor (Se/se)

In 1926, it was found that ABH antigens were present, in soluble form, in seminal fluid and saliva. It was observed that the ability to secrete those antigens was genetically independent of ABO.

The locus controlling the secretion of ABH substances is called Secretor. The capacity to secrete (Se) is inherited as a dominant trait over the non-secretor phenotype (se). Se and se are alleles of the endodermal α1,2-fucosyltransferase gene (FUT2). Secretor-transferase, the product of FUT2, is active in tissue of endodermal origin and is responsible for Type 1 and 2 H structures. In secretor individuals of the appropriate ABO group, ABH antigens are detected in secretions of the goblet cells and mucous glands of the gastrointestinal tract (saliva, gastric juice, bile, meconium), genitourinary tract (seminal fluid, vaginal secretions, ovarian cyst fluid, urine), and respiratory tract, as well as milk, sweat, tears and amniotic fluid. The Se allele is present in the majority of the population (Race & Sanger, 1975).

In non-secretors se determines the absence of H substance in secretions. Therefore, A and B transferases, which are not under the control of the secretor gene, are not able to catalyze the production of A and B substances in body fluids of non-secretors who lack the H antigen, their acceptor substrate.

FUT2 gene consists of two exons with the entire coding sequence contained in the second exon and encodes a 332 amino acid long enzyme with a higher affinity to Type 1 acceptor substrates. An additional isoform with 11 more amino acid residues at the N-terminus has also been described. The allele containing the nonsense mutation at codon 143 is the most common non-secretor allele of FUT2. That mutation generates a stop codon and produces an early translation termination resulting in a null enzymatic activity. (Kelly et al., 1995; Spitalnik & Spitalnik, 2000)

7. Evolution genetics and homologous genes

The ABO gene has been conserved throughout evolution. Primates present a 95% of amino acid conservation among the ABO transferases. Comparing the partial nucleotide and deduced amino acid sequences of the ABO gene in samples of several species of primates with the human ABO gene, it was found that A to B divergence could have occurred at least in three different occasions during the ABO gene evolution in primates (Saitou & Yamamoto, 1997).

In addition, the ABO gene repertoire of alleles varies between humans and the other primates. For example, in chimpanzees there are only A or O groups, and in gorillas only the B type is found, in contrast with the A, B, AB or O groups in human. ABO groups exist in other mammals other than primates as well. For instance, pigs only show an AO polymorphism (Yamamoto & Yamamoto, 2001), and the mouse ABO gene encodes for an enzyme with dual specificity that is capable of synthesizing both A and B antigens *in vitro*, although in animal tissues the A antigen is primarily detected (Yamamoto et al., 2001). Currently, and thanks to DNA sequencing efforts, ABO orthologous genes have been found in a total of 45 vertebrate species.

In addition to A and B transferases, additional enzymes exist with similar specificities. The genes encoding these glycosyltransferases have some similarity and are evolutionary related with the ABO gene. They are classified into the α1,3- Gal(NAc) transferase family (or GT6

family). They are α1,3-galactosyltransferase (α1,3GalT), isogloboside b3 synthase (iGb3S), and Forssman glycolipid synthase (FS).

α1,3GalT transferase is encoded by the GGTA1 gene and catalyses the transfer of galactose to another galactose to form the α-galactosyl epitope (Galα1-3Gal-). As opposite to A and B transferases, α1,3GalT utilizes acceptor substrates lacking a fucose linked to the galactose. This enzyme activity is present in many mammalian species including some primates, but excluding Old World monkeys and anthropoid apes, such as humans. These species instead possess the antibody against the α-galactosyl epitope (Macher & Galili, 2008). On humans the GGTA1 gene was shown to contain frameshift and nonsense mutations, abolishing the enzymatic activity (Shaper et al., 1992).

IGb3S synthesizes iGb3 ceramide (Galα1-3Galβ1-4GlcCer) and it is encoded by the A3GALT2 gene. This enzyme transfers a galactose using the UDP-galactose as a donor substrate (Keusch et al., 2000). Conversely, FS is encoded by the GBGT1 gene and is responsible for the synthesis of Forssman antigen (GalNAcα1-3GalNAcβ1-3Galα1-4Galβ1-4GlcCer) using a UDP-GalNAc as a donor substrate (Haslam & Baenziger, 1996).

Apart from vertebrates some bacteria are also capable of synthesizing A or B antigens. In the case of *Escherichia coli* strain O86 high B activity was detected on its *O*-lipopolysaccharide antigen. Non-vertebrate A/B transferases genes have been identified in many other bacteria and also in one cyanophage. Based on the fact that there are no homologous genes found in species between vertebrates and bacteria, the possibility of horizontal transfer was proposed (Brew et al., 2010).

8. Natural antibodies against ABH

ABO is the only blood group system that in a natural and consistent manner has antibodies present in sera of people who lack the corresponding antigen from their red blood cells. With the exception of newborn infants under 5 months, deviations from this rule are extremely rare and related to disease. These antibodies are detected at about 3 months and increase their titer until the 5th to 10th year of life. Neonates may present the IgG type of ABO antibodies that have maternal origin, because IgG antibodies can cross the placenta. However in some occasions the fetus can produce by himself the IgM type of ABO antibodies. In adults they are mostly IgM although some may be IgG or IgA. The ABO antibodies may also be found in various body fluids including saliva, milk, cervical secretions, tears, and cysts.

The widely held hypothesis to explain the presence of these alloantibodies is that they are formed in response to terminal carbohydrates that share structural homology with A and B antigens present in the organism. These could derive from bacteria cell walls from normal intestinal microbial flora or be of animal origin and introduced through the diet. This view is supported by the fact that the levels of anti-A and anti-B antibodies seem to be influenced mostly by environmental factors, and genetics have a minor role.

Sera from A individuals contain anti-B antibody while B individuals' sera contain two types of antibody against A antigens. The first is anti-A and the second one is specific towards A_1 RBCs. Anti-A reacts with both A_1 and A_2 cells whereas the second only does with A_1 RBCs. Anti-A_1 is also present in some A_2 and A_2B individuals (Landsteiner & Levine, 1926). Group O people produce an antibody, anti-A,B able to cross-react with both A and B RBCs. It has

been proposed that this antibody binds to a common structure shared by A and B antigens. This has been confirmed using human monoclonal analysis. Anti-A,B isotype is mainly IgG but some IgM or IgA may be present (Klein et al., 2005). Bombay (O_h) and para-Bombay type individuals also present a very potent anti-H antibody. That is the reason they can only be transfused with blood of their own type as RBCs from all the main groups will be destroyed due to the presence of the H antigen (Le Pendu et al., 1986).

9. ABO typing

In the reverse typing, the detection of antibodies against the A or B antigens in sera is performed using RBCs of known type (A_1 and B) that have been available for many years. But, forward ABO typing procedures changed completely with the invention of the hybridoma technology and the production of monoclonal antibodies. Reagents to better type blood donors were created. Nowadays, monoclonal antibodies to detect A and B antigens are routinely used in transfusion and clinical medicine and detailed descriptions are found in specialized reports. Very potent anti-A antibodies are able to agglutinate A_x RBCs helping in the detection of rare subgroups. They have also been very helpful in determining the structure of the precursor chains bound to A determinants. Also anti-B, anti-A,B and anti-H have been produced.

Lectins are proteins of non-immune origin able to bind sugars and therefore agglutinate cells or precipitate glycoconjugates carrying specific saccharides. Their binding to glycans can be inhibited by mono- or oligosaccharides. The nature of these sugar inhibitors is used to identify the specificity of the lectin as it is assumed that they are binding to the same site as the cell surface antigens. For reviews see (Bird, 1989; Nilsson 2007).

DBA, from *Dolichos biflorus* is specific for terminal N-acetylgalactosamine and has been extensively used to differentiate A_1 from A_2 subgroup RBCs. At precise dilutions A_1 and A_1B cells react positively while A_2 and A_2B do not. This property has been attributed to the avidity of the lectin rather than to qualitative differences between A_1 and A_2 antigens (Furukawa et al., 1985). There are fewer examples of B-specific lectins. As the specificity of these lectins depends on the terminal D-galactose determinant, they may cross-react with other antigens containing similar residues, i.e P, P1 and P^k (Voak et al., 1974). The most used reagent to detect secretor status in saliva from O group individuals is *Ulex europaeus* lectins which recognize the H antigen. Two lectins are present in the seeds of this species: UEA I is inhibited by L-fucose while UEA II is not. UEA II seems to recognize not only the terminal L-fucose but also a subterminal N-acetylglucosamine. The fucose requirement for reactivity of both lectins was corroborated by their failure to react against α-L-fucosidase-treated O cells (Matsumoto & Osawa, 1970).

Technical improvements have also allowed the detection and quantification of the antigens and the correspondent antibodies by other techniques than hemagglutination, such as cytofluorometry or ELISA and are being used to detect ABO histo-blood antigens in other organs and tissues.

10. ABO genotyping

Within the immunology related fields, HLA and ABO were two of the first genes to which DNA-based genotyping was applied. Many alleles encoding for variants of the main ABO alleles have been discovered and annotated and also in many cases their frequency in

various world populations is also known. In any case, ABO typing based only on DNA techniques faces a very unique drawback. The O alleles are mostly the result of inactivating mutations of A[1]. Only those which are known can be detected by regular genotyping methods that otherwise will miss any novel ones. Complete sequencing of the donor/recipient genome is about to solve the problem of undetected mutations which arise from only sequencing some exons or RFLP strategies. But still, there are cases in which mutations in non-coding regions can produce aberrant messengers, as the formation of a new splicing site, or changes in expression levels if they are located in promoter or enhancer regions. Confusion over non-deleterious SNPs and novel mutations is going to arise with the introduction of these new technologies, and therefore forward and/or reverse typing are not going to disappear from blood bank facilities (Anstee, 2009; Reid & Denomme 2011).

Numerous methods have been established to determine the ABO genotype from genomic DNA (reviewed in (Olsson et al., 2001)). They are mostly designed to detect three to six of the most common alleles but many are not able to predict many subgroup, nondeletional, *cis*-AB and B(A) alleles, or hybrid alleles. A wrongly assigned blood type can be of serious consequence not only in blood transfusion but also for transplantation. Screening strategies taking into account these rare alleles have been implemented (Hosseini-Maaf et al., 2007). But for the most of the small/medium clinical setting microsequencing has been developed allowing a faster and reliable identification of the six major alleles. High-throughput techniques are able to detect more described mutations/alleles but they are considerably more expensive (Ferri & Pelotti, 2009).

11. Non-infectious adverse effects of ABO incompatibility

Many efforts have been devoted to avoid the transmission of pathogens during transfusion. But incompatibility barriers associated with ABO may cause clinical symptoms derived from mismatched ABO phenotypes.

11.1 ABO hemolytic disease of the newborn

Rh antigens are the most common blood group antigens associated with hemolytic disease of the newborn (HDN) but this disease also occurs as a result of ABO incompatibility between group O mothers carrying a group A, B or AB fetus (recently reviewed by Roberts (Roberts, 2008)). Even though the ABO incompatibility between mother and fetus should affect around a 20% of all pregnancies (in the case of European descent parents) only in very few instances they become symptomatic. Moreover, in many of those manifested cases this incompatibility only results in very mild symptoms and requires no treatment. In a small number of cases, phototherapy or antibody-inhibition by soluble oligosaccharides have been used.

A very minor fraction of these mothers produces a high quantity of IgG antibodies in place of the common IgM antibodies. The IgG isotype can pass through the placenta to the fetal circulation causing hemolysis of fetal RBCs and therefore fetal anemia and HDN. Although very uncommon, cases of ABO HDN have been reported in infants born to mothers with blood groups A and B. In contrast to Rh disease, about half of the cases of ABO HDN occur in a firstborn baby and ABO HDN does not become much severer after further pregnancies.

11.2 Erroneous transfusion

Even now, erroneous ABO incompatible transfusion is still an important cause for morbidity and mortality associated with transfusions, together with other non-ABO hemolytic transfusion reactions (HTR), transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and bacterial contamination. The year 2010 report from the United Kingdom SHOT hemovigilance system showed a 2% of all the cases of incompatible transfusion corresponding to the ABO system (SHOT, 2010). A similar report from the USA FDA published in 2009 indicated that 9% of all fatal cases during transfusion were due to ABO mismatched HTR (FDA, 2009). Fortunately, many reports have shown that about 50 percent of ABO-mismatched recipients do not show any obvious sign of a transfusion reaction. The reason for this lack of symptoms is not known but if resistance mechanisms are involved, their elucidation could lead to the improvement of transplantation strategies.

Studies on ABO-compatible, but not ABO-identical, blood transfusions have shown an increased risk of death in recipients of ABO-mismatched platelet concentrates. As mentioned before, platelets also express ABH antigens in variable amounts. It has been shown though that platelets coming from A_2 individuals do not express H or A antigens and can be used as "universal". The biochemical reason for this phenomenon is not known yet (Cooling et al., 2005).

11.3 ABO mismatched transplantations

ABO-mismatching has also been investigated in transplantation recipients. In the case of hematopoietic stem cell transplantation, ABO incompatibility has not been associated with a shortened overall survival or increased mortality related to transplantation. However, transplantation of solid organs with ABO-incompatibility has a more modest success rate depending on the age of the recipient. Infants tolerate much better this incompatibility as demonstrated in heart transplantation probably due to B-cell immature response. Immunosuppressive drugs are the hallmark treatment after any kind of transplantation as they are able to reduce or eliminate rejection reactions. These molecules together with apheresis and monoclonal antibody therapies are of help in ABO-mismatched transplantation (Nydegger et al., 2005; Nydegger et al., 2007).

12. ABO and diseases

Many associations have been reported between specific ABO alleles and different susceptibility to several diseases such as vascular and cardiovascular diseases, diverse infections, and also cancer. For many years studies compared the incidence of a disease within each of the blood groups and it became apparent that some kind of association existed between some diseases and particular blood types. More recently genome-wide association studies have taken over and in a bias-free manner have linked polymorphisms of the ABO locus to different diseases (reviewed in Yamamoto et al., 2011)(Fig. 3).

Relating cardiovascular and vascular disease it is known that the ABO groups are a major determinant modulating the plasma levels of two coagulation factors: factor VIII (FVIII) and von Willebrand factor (vWF). Non-O blood group individuals have approximately 25%

lower levels of these glycoproteins. It was already known that there was a higher incidence of both arterial and venous thrombotic disease in A, B or AB individuals compared with O group individuals. This has been confirmed by GWAS results showing decreased risk for venous thromboembolism among individuals of O and A_2 groups (Tregouet et al., 2009).

There have also been studies aimed to understand different associations of ABO with pathogenic infections like Noroviruses because of the fact that many bacteria or viruses utilize glycosylated proteins as cell surface receptors for attachment. The interactions between host receptors and pathogen predict that these associations are very dependent on the receptor selectivity. Actually, many classical etiological studies identified links between ABO and peptic ulcer, cholera, or malaria (Mourant et al., 1978). These associations are currently being reassessed by the newer genomic approaches. In the case of malaria, a recent GWAS has not found strong association with ABO although the same samples exhibited the association by targeted analysis (Jallow et al., 2009).

But one of the most striking associations found is the increased susceptibility of non-O blood type individuals to pancreatic cancer. For both stomach and pancreatic cancer this difference in incidence was already known from targeted studies. Recently though, in the case of pancreatic cancer a GWAS has confirmed this association and ranked first a single nucleotide polymorphism in the ABO gene discriminating O- and non-O alleles with the highest score (Amundadottir et al., 2009). It is obvious that the presence of non-O alleles does not cause cancer, but nonetheless they might be favoring the carcinogenic process in a subtle but steady manner.

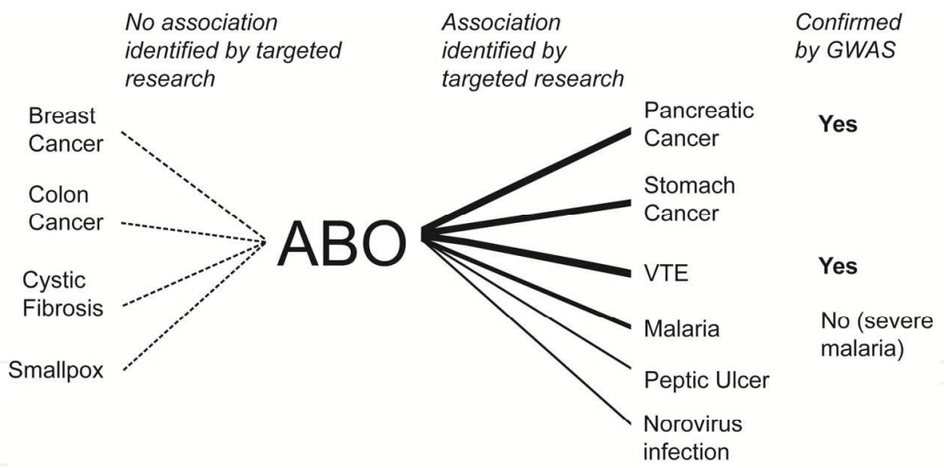

Fig. 3. Diseases associated with ABO polymorphisms were first detected by targeted research and some of these associations have been confirmed by GWAS. Other studies also found no association with other diseases.

As we mentioned before, the expression of ABH antigens is not constant. It undergoes alterations during cellular differentiation, development and aging as well as pathologic phenomena, as occurs in carcinogenesis. In the case of ABO it has been known for many years that tumors may reduce the expression of A or B antigens and that process is part of the global changes that cancer cause in glycosylation (Hakomori, 1999). Some of these

changes are already being used as diagnostic markers but as more studies are brought forward more are going to be added.

13. Enzyme-converted O RBCs

O RBCs can be transfused to individuals of any ABO group type as they are not going to react with any of the alloantibodies. Therefore, in case of a surplus of A or B blood it would be advantageous to be able to convert it to O. One of the most promising strategies to achieve this has been the use of glycosidases able to enzymatically remove the terminal sugar (N-acetylgalactosamine in the case of A or galactose for B). There have been advancements with the use of bacterial glycosidases and this line of research is still being pursued actively (Olsson & Clausen, 2008).

14. Conclusion

The ABO histo-blood group system is a major player in transfusion/transplantation and regeneration medicine. For years, investigations in this field have been pushing forward developments in different scientific areas. New typing procedures and strategies to cross the ABO incompatibility barriers are improving blood banking and transfusion. Moreover, basic research focused on this system contributes to a better understanding of a range of topics, from genomics to pathological processes. We anticipate that newer technologies will bring individual genome sequencing to a daily routine in the coming years and that will affect not only ABO genotyping but also many other medical issues. GWAS will increase the links of ABO to other diseases, giving the opportunity to researchers to start to tackle one of the most fundamental, and unanswered questions about ABO, the function of the antigens in physiological and pathological conditions by studying the molecular mechanisms underlying those associations.

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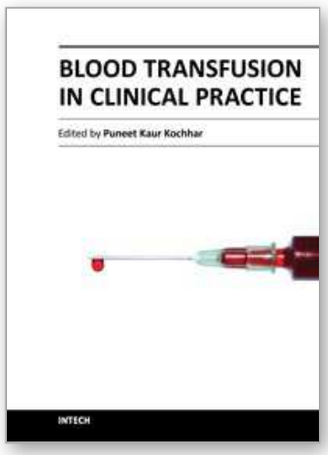

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Blood Transfusion in Clinical Practice focuses on the application of blood transfusion in different clinical settings. The text has been divided into five sections. The first section includes a chapter describing the basic principles of ABO blood group system in blood transfusion. The second section discusses the use of transfusion in various clinical settings including orthopedics, obstetrics, cardiac surgery, etc. The third section covers transfusion transmitted infections, while section four describes alternative strategies to allogenic blood transfusion. The last section speculates over immunomodulatory effects of blood transfusion.

How to reference

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