DEPARTMENT OF ZOOLOGY

STUDENT STUDY PROJECTS

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TITLE: IDENTIFY THE BLOOD GROUPS BY ANTIBODIES AND ANTIGENS IN THE BLOOD"

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Aims and Objectives;

The accurate grouping of blood is very important when it comes to having a blood transfusion. If blood is given to a patient that has a blood type that is incompatible with the blood type of the blood that the patient receives, it can cause intravenous clumping in the patient's blood which can be fatal.
Your blood group is identified by antibodies and antigens in the blood. Antibodies are proteins found in plasma. They're part of your body's natural defences. They recognise foreign substances, such as germs, and alert your immune system, which destroys them.

- Be able to name the two main "naturally occurring" antibodies to red cell antigens.
- Be able to tell which of these two antibodies would be found in individuals of each ABO type, and briefly explain why ordinarily they would or would not be present.
- Be able to explain why the ABO system is the most important red cell blood group system for transfusion therapy.
- Given the Rh phenotype of a mother and her fetus, be able to state whether the baby may be at risk of developing hemolytic disease of the newborn (HDN) due to anti-Rh antibodies, and why (or why not). Be able to state the immunoglobulin class responsible for HDN, and give the reason that other classes of immunoglobulin do not cause HDN.
- Be able to diagram the direct antiglobulin test (the Coombs test), indicating the main components and their source (patient vs. reagent). Be able to state what the direct antiglobulin test is capable of detecting. Be able to diagram the indirect antiglobulin test and state the major purpose for the indirect antiglobulin test.
- Be able to list the three essential steps in blood compatibility testing, and the purpose of each step.
- In an emergency situation, be able to indicate what kind of blood is given, if necessary, before typing is complete, and what kind of blood is given, if necessary, before cross-matching is complete.

Introduction:

The discovery of the ABO blood group, over 100 years ago, caused great excitement. Until then, all blood had been assumed to be the same, and the often tragic consequences of blood transfusions were not understood. As our understanding of the ABO group grew, not only did the world of blood transfusion become a great deal safer, but scientists could now study one of the first human characteristics proven to be inherited. A person's ABO blood type was used by lawyers in paternity suits, by police in forensic science, and by anthropologists in the study of different populations.

The ABO blood group antigens remain of prime importance in transfusion medicine—they are the most immunogenic of all the blood group antigens. The most common cause of death from a blood transfusion is a clerical error in which an incompatible type of ABO blood is transfused. The ABO blood group antigens also appear to have been important throughout our evolution because the frequencies of different ABO blood types vary among different populations, suggesting that a particular blood type conferred a selection advantage (e.g., resistance against an infectious disease.)

However, despite their obvious clinical importance, the physiological functions of ABO blood group antigens remain a mystery. People with the common blood type O express neither the A nor B antigen, and they are perfectly healthy. Numerous associations have been made between particular ABO phenotypes and an increased susceptibility to disease. For example, the ABO phenotype has been linked with stomach ulcers (more common in group O individuals) and gastric cancer (more common in group A individuals). Another observation is that individuals with blood type O tend to have lower levels of the von Willebrand Factor (vWF), which is a protein involved in blood clotting.

Result & Discussion:

At the beginning of the 20th century an Austrian scientist, Karl Landsteiner, noted that the RBCs of some individuals were agglutinated by the serum from other individuals. He made a note of the patterns of agglutination and showed that blood could be divided into groups. This marked the discovery of the first blood group system, ABO, and earned Landsteiner a Nobel Prize.

Landsteiner explained that the reactions between the RBCs and serum were related to the presence of markers (antigens) on the RBCs and antibodies in the serum. Agglutination occurred when the RBC antigens were bound by the antibodies in the serum. He called the antigens A and B, and depending upon which antigen the RBC expressed, blood either belonged to blood group A or blood group B. A third blood group contained RBCs that reacted as if they lacked the properties of A and B, and this group was later called "O" after the German word "Ohne", which means "without". The following year the fourth blood group, AB, was added to the ABO blood group system. These RBCs expressed both A and B antigens.

In 1910, scientists proved that the RBCs antigens were inherited, and that the A and B antigens were inherited codominantly over O. There was initially some confusion over how a person's blood type was determined, but the puzzle was solved in 1924 by Bernstein's "three allele model".

The ABO blood group antigens are encoded by one genetic locus, the ABO locus, which has three alternative (allelic) forms—A, B, and O. A child receives one of the three alleles from each parent, giving rise to six possible genotypes and four possible blood types (phenotypes).

Nomenclature

- Number of ABO blood group antigens: 4
- ISBT symbol: ABO
- ISBT number: 001
- Gene symbol: ABO
- Gene name: ABO blood group (A transferase, α1,3-N-acetylgalactosaminyltransferase; B transferase, α1,3-galactosyltransferase)

ABO phenotypes

The four basic ABO phenotypes are O, A, B, and AB. After it was found that blood group A RBCs reacted differently to a particular antibody (later called anti-A1), the blood group was divided into two phenotypes, A_1 and A_2. RBCs with the A_1 phenotype react with anti-A1 and make up about 80% of blood type A. RBCs with the A_2 phenotype do not react with anti-A1 and they make up about 20% of blood type A. A_1 red cells express about 5 times more A antigen than A_2 red cells, but both types of red cell react with anti-A, and as far as transfusion purposes are concerned, the A_1 and A_2 blood groups are interchangeable.

There are many other subgroups of blood group A in which RBCs tend to weakly express the A antigen, whereas weak variants of the blood group B phenotype are rare (2).

The immune system forms antibodies against whichever ABO blood group antigens are *not* found on the individual's RBCs. Thus, a group A individual will have anti-B antibodies and a group B individual will have anti-A antibodies. Blood group O is common, and individuals with this blood type will have both anti-A and anti-B in their serum. Blood group AB is the least common, and these individuals will have neither anti-A nor anti-B in their serum.

ABO antibodies in the serum are formed naturally. Their production is stimulated when the immune system encounters the "missing" ABO blood group antigens in foods or in micro-organisms. This happens at an early age because sugars that are identical to, or very similar to, the ABO blood group antigens are found throughout nature.

The ABO locus has three main alleleic forms: A, B, and O. The A allele encodes a glycosyltransferase that produces the A antigen (N-acetylgalactosamine is its immunodominant sugar), and the B allele encodes a glycosyltransferase that creates the B antigen (D-galactose is its immunodominant sugar).

The O allele encodes an enzyme with no function, and therefore neither A or B antigen is produced, leaving the underlying precursor (the H antigen) unchanged. These antigens are incorporated into one of four types of oligosaccharide chain, type 2 being the most common in the antigen-carrying molecules in RBC membranes. Some of the other enzymes involved in the earlier stages of ABO antigen synthesis are also involved in producing antigens of the Hh blood group and the Lewis blood group.

Expression

Although the ABO blood group antigens are regarded as RBC antigens, they are actually expressed on a wide variety of human tissues and are present on most epithelial and endothelial cells.

Each human RBC expresses about 2 million ABO blood group antigens. Other blood cells, such as T cells, B cells, and platelets, have ABO blood group antigens that have been adsorbed from the plasma. In individuals who are "secretors", a soluble form of the ABO blood group antigens is found in saliva and in all bodily fluids except for the cerebrospinal fluid.

A number of illnesses may alter a person's ABO phenotype. Patients can "acquire" the B antigen during a necrotizing infection during which bacteria release an enzyme into the circulation that converts the A1 antigen into a B-like antigen (3). During this time, patients should not receive blood products that contain the B antigen because their sera will still contain anti-B. Once the underlying infection is treated, the patients' blood groups return to normal.

Illness can also cause patients to "lose" ABO blood group antigens. Any disease that increases the body's demand for RBCs may weaken the expression of ABO blood group antigens, e.g., thalassemia. In addition, ABO blood group antigens can be altered by hematological cancers that can modify the sugar chains that bear the ABO blood group antigens, lending to the use of the A and B antigens as tumor markers for acute leukemia, myeloproliferative disorders, and myelodysplasia.

Function of the A and B antigens

The functions of the ABO blood group antigens are not known. Individuals who lack the A and B antigens are healthy, suggesting that any function the antigens have is not important, at least not in modern times.

Diseases associated with ABO blood group antigens

No diseases are known to result from the lack of expression of ABO blood group antigens, but the susceptibility to a number of diseases has been linked with a person's ABO phenotype. Such correlations remain controversial and include the observation that gastric cancer appears to be more common in group A individuals (4), whereas gastric and duodenal ulcers occur more often in group O individuals (5).

A clear correlation has been established between the ABO phenotype and the level of two proteins involved in blood clotting; factor VII (FVIII) and von Willebrand factor (vWF) (6). Blood group O individuals have about 25% less FVIII and vWF in their plasma. It is well established that low levels of FVIII and vWF are a cause of excess bleeding, and therefore it may

also be the case that increased levels make clotting more likely, increasing the risk of both arterial (ischemic heart disease) and venous (thromboembolic disease) problems. Indeed, non-group O individuals have been shown to be at an increased risk of both arterial and venous disease (6).

Conclusion:

Transfusion reactions

The routine practice of blood typing and cross matching blood products should prevent adverse transfusion reactions caused by ABO antibodies. However, clerical error can result in "the wrong blood" being transfused into a patient, an error which can result in the death of the patient (7, 8).

If a recipient who has blood group O is transfused with non-group O RBCs, the naturally occurring anti-A and anti-B in the recipient's serum binds to their corresponding antigens on the transfused RBCs. These antibodies fix complement and cause rapid intravascular hemolysis, triggering an acute hemolytic transfusion reaction that can cause disseminated intravascular coagulation, shock, acute renal failure, and death.

Anti-A1 is a less significant cause of transfusion reactions and does not appear to fix complement.

Hemolytic disease of the newborn

Most cases of hemolytic disease of the newborn (HDN) that arise from an ABO incompatibility require no treatment. Cases of severe hemolysis that require exchange transfusions are less common, and fetal hydrops is rare (9).

HDN caused by ABO antibodies occurs almost exclusively in infants of blood group A or B who are born to group O mothers (10). This is because the anti-A and anti-B formed in group O individuals tend to be of the IgG type (and therefore can cross the placenta), whereas the anti-A and anti-B found in the serum of group B and A individuals, respectively, tends to be of the IgM type. Although uncommon, cases of HDN have been reported in infants born to mothers with blood group A2 (11) and blood group B (12).

HDN tends to be relatively mild in nature mainly because fetal RBCs don't express adult levels of A and B antigens. However, the strength of fetal ABO blood group antigens can vary, and therefore the degree of hemolysis and hence the severity of HDN can be unpredictable (13). Early studies suggested that the race of a neonate was a risk factor for developing ABO HDN (14). However, later studies showed that the prevalence of disease that required treatment did not differ significantly among Asian, Black, Hispanic, and Caucasian infants (15).

Gene

The ABO locus encodes specific glycosyltransferases that synthesize A and B antigens on RBCs. For A/B antigen synthesis to occur, a precursor called the H antigen must be present. In RBCs, the enzyme that synthesizes the H antigen is encoded by the H locus (FUT1). In saliva and other bodily secretions, the enzyme that synthesizes the H antigen is encoded by the Se locus (FUT2).

The ABO locus

The ABO locus is located on chromosome 9 at 9q34.1-q34.2. It contains 7 exons that span more than 18 kb of genomic DNA. Exon 7 is the largest and contains most of the coding sequence. Exon 6 contains the deletion that is found in most O alleles and results in a loss of enzymatic activity.

The A and B alleles differ from each other by seven nucleotide substitutions, four of which translate into different amino acids in the gene product (R176G, G235S, L266M, G268A). The residues at positions 266 and 268 determine the A or B specificity of the glycosyltransferase they encode (16).

The O allele differs from the A allele by deletion of guanine at position 261. The deletion causes a frameshift and results in translation of an almost entirely different protein that lacks enzymatic activity (16).

There are many variant ABO alleles that encode a number of variant ABO phenotypes, but they do not encode specific antigens other than the A and B antigens. For example, weak A subgroups, such as A_3, A_x, and A_{el}, express the A antigen, and weak B subgroups, such as B_3 and B_x, express the B antigen (2).

The H locus (FUT1)

The H locus is located on chromosome 19 at 19q13.3. It contains three exons that span more than 5 kb of genomic DNA, and it encodes a fucosyltransferase that produces the H antigen on RBCs.

Individuals who are homozygous for null alleles at this locus (h/h) do not produce H antigen, and because the H antigen is an essential precursor to the ABO blood group antigens, they cannot produce A and B antigens. Therefore, their serum contains anti-A and anti-B, in addition to potent anti-H. This rare phenotype of H-deficient RBCs is called the "Bombay phenotype" (O_h) after the city in which it was first discovered. Individuals with the Bombay phenotype are healthy, but if they ever needed a blood transfusion, the antibodies in their serum would place them at a high risk of having an acute hemolytic transfusion reaction. This can be avoided by using only blood products from a donor who also has the Bombay phenotype (usually a relative).

The Se locus (FUT2)

The Se locus is located on chromosome 19 at 19q13.3. It contains two exons that span about 25 kb of genomic DNA.

The Se locus encodes a specific fucosyltransferase that is expressed in the epithelia of secretory tissues, such as salivary glands, the gastrointestinal tract, and the respiratory tract. The enzyme it encodes catalyzes the production of H antigen in bodily secretions.

"Secretors" have at least one copy of the Se gene that encodes a functional enzyme—their genotype is Se/Se or Se/se. They secrete H antigen which, depending on their ABO genotype, is then processed into A and/or B antigens.

Non-secretors are homozygous for null alleles at this locus (se/se). They are unable to produce a soluble form of H antigen and hence do not produce A and B antigens.

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