FEATURED ARTICLE

ABO Blood Groups

SUSAN OFFNER

ABSTRACT

The molecular basis of ABO blood groups is now known and presents an interesting and important teaching opportunity.

Key Words: *ABO blood group; molecular basis of ABO blood groups; oligosaccharides.*

The Molecular Biology of ABO Blood Groups

Human ABO blood groups were first described by Karl Landsteiner in 1900. The studies were done in the early days of surgery when some surgical patients mysteriously died after receiving a transfusion of what we now know was blood of the wrong type. We now know the molecular biology of the ABO blood groups, both at the biochemical level and at the DNA level. Since students have all heard about ABO blood types, this offers a way to show students how molecular biology affects a well-known phenotype. This article presents two important diagrams. Figure 1 shows the oligosaccharides on the outside of red blood cells that are responsible for ABO blood types. Figure 3 shows the actual sequence of amino acids in the proteins of people with Type A, Type B, and Type O blood and explains how they account for the observed blood types. These diagrams give students a new appreciation of how genes code for proteins and proteins determine phenotype.

We now know the molecular biology of the ABO blood groups, both at the biochemical level and at the DNA level.

The ABO Phenotype

Human beings have four ABO blood types: A, B, AB, and O. Each of these types is determined by the oligosaccharides on the glycocalyx of the cell membrane of red blood cells. An oligosaccharide is a molecule consisting of some (about 4–15) monosaccharides held together by covalent bonds. The glycocalyx is located on the outside of the cell membrane and consists of proteins, glycoproteins, and glycolipids. The immune system recognizes and responds to the glycocalyx. More information is included in the Appendix.

The oligosaccharides involved in ABO blood types are shown in Figure 1. In a single red blood cell, between 1 and 2 million of these oligosaccharides are attached to a protein called "band 3," which is an anion transporter. Another 500,000 of these oligosaccharides are attached to the glucose transporter, the protein that lets glucose into the cell. Still another 500,000 oligosaccharides are attached to lipids and are therefore part of glycolipid molecules (Viel, 2009).

Genetics of the ABO Antigens

Oligosaccharides, of course, are not directly inherited. However, each monosaccharide in an oligosaccharide is added to the oligosaccharide by a specific enzyme. These enzymes are coded for by genes, which are inherited and, of course, subject to mutation and variation. In the case of ABO blood types, there is a locus near the tip of the long arm of chromosome 9 that contains a gene that codes for these enzymes, as shown in Figure 2. This locus is technically called "9q34.2." There are three possible alleles at this locus:

1. The type A (I^A) allele codes for an enzyme called A transferase. A transferase adds a molecule of N-acetylgalactosamine to the end of the oligosaccharide, as shown in Figure 1.
2. The type B (I^B) allele codes for an enzyme called "B transferase," which adds a molecule of galactose to the end of the oligosaccharide, as shown in Figure 1.

The American Biology Teacher, Vol. 77, No 8, pages. 583–586, ISSN 0002-7685, electronic ISSN 1938-4211. DOI: 10.1525/abt.2015.77.8.4.

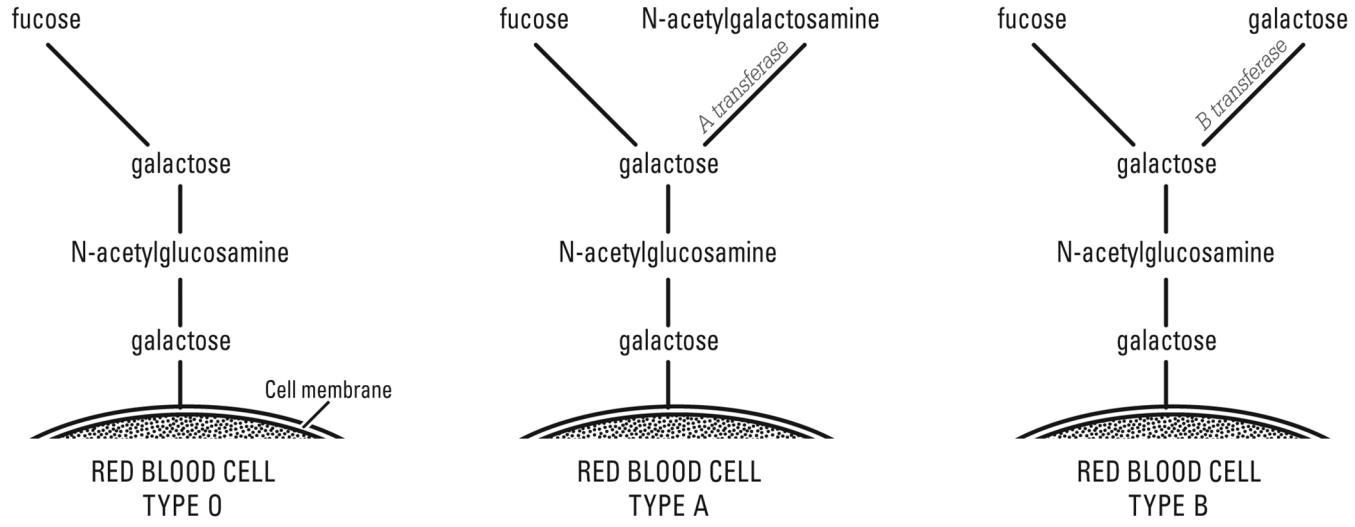

Figure 1. The oligosaccharides involved in ABO blood types, located on the outside of the cell membrane of red blood cells. Some are attached to proteins, and others are attached to glycolipids (see text).

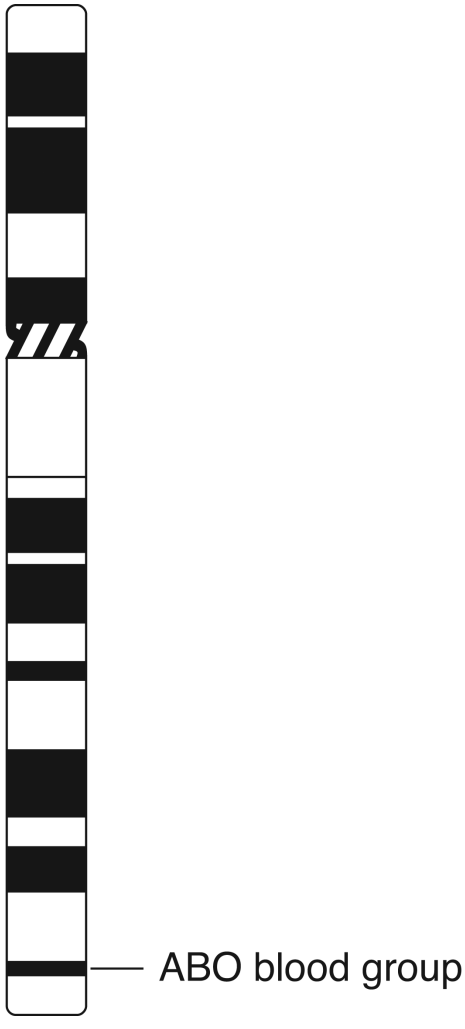

Figure 2. The location of the genes coding for ABO blood types on human chromosome number 9. There are a total of ~1742 genes on chromosome 9 (NCBI databases; http://www.ncbi.nlm.nih.gov/projects/mapview/).

3. The type O (i) allele, as we will see later, does not code for an active enzyme; therefore, no additional monosaccharide is added.

I^A and I^B are both dominant to Type O (i), since a person with one I^A allele and one i allele will make enough A transferase so that their red blood cells will have N-acetylgalactosamine at the end of their oligosaccharides. Similarly, a person with one I^B allele and one type O (i) allele will have enough B transferase so that their red blood cells will have galactose at the end of their oligosaccharides. A person with type AB blood has one I^A allele and one I^B allele and therefore makes both A transferase and B transferase. They will have some oligosaccharides ending in N-acetylgalactosamine and some ending in galactose.

O This System Explains Transfusion Compatibilities

This system also explains the compatibility of different blood types during transfusions. These genetically inherited oligosaccharides serve as antigens on the surface of red blood cells, alerting the immune system to the possibility of the presence of a foreign substance.

Individuals produce antibodies directed against the antigen (A or B) that is not displayed at the surface of their cells. The only exception is that, since O antigen is really just a lack of A or B antigens (Figure 1), nobody makes O antibodies, so type O blood does not trigger an immune response in a person, regardless of their blood type. This is why Type O is the universal donor.

But individuals with the O blood type do produce antibodies to both A and B antigens, so they can't receive these red blood cells. If the red blood cells have the A antigen, as in a Type A person, the immune system produces antibodies to the B antigen. If the red blood cells have the B antigen, as in a Type B person, the immune system produces antibodies to the A antigen. If the red blood cells have both A and B antigens, as in a Type AB person, the immune system does not make antibodies to either of these. Individuals

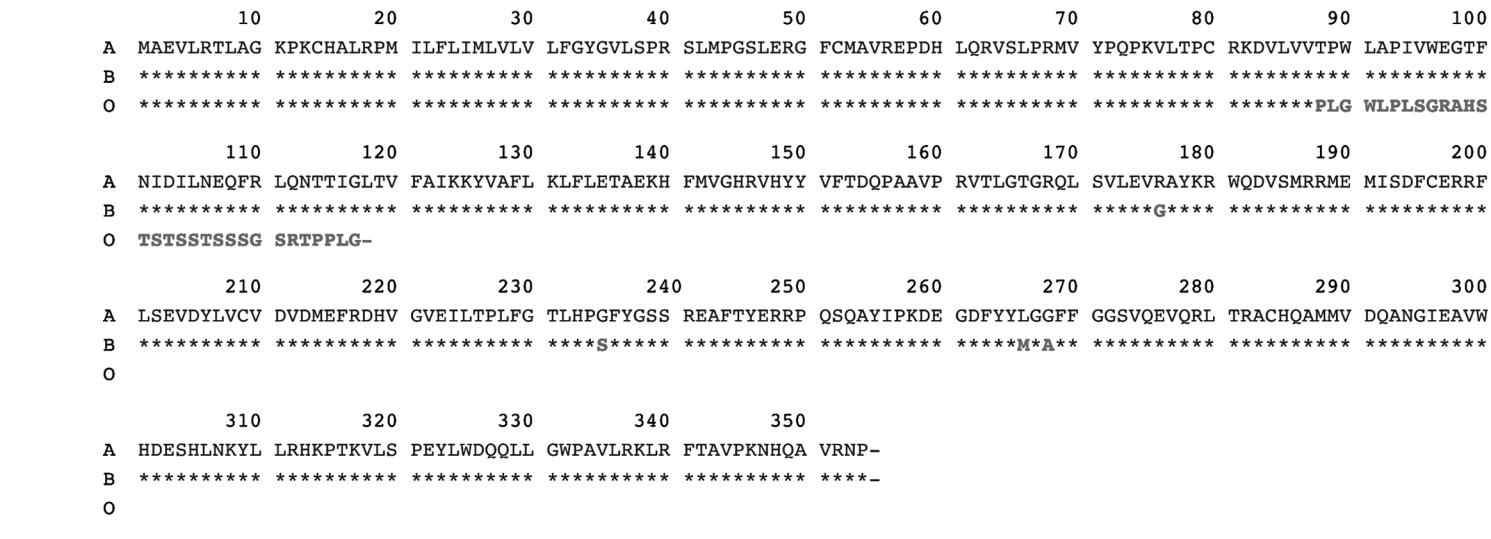

Figure 3. The order of amino acids in the proteins coded for by the three alleles of the ABO blood-type locus. Single-letter abbreviations for the amino acids are used throughout. The top line, labeled "A," shows the order of amino acids in the A transferase enzyme. The middle line, labeled "B," shows the order of amino acids in the B transferase enzyme. Stars indicate that the amino acid is identical to the amino acid in the A transferase enzyme. The bottom line, labeled "O," shows the order of amino acids in the protein fragment coded for by the O gene. Stars indicate that the amino acid is identical to the amino acid in the A transferase enzyme. The dash at the end of each protein indicates the end of the protein. Single-letter abbreviations for the amino acids are as follows: A = alanine, C = cysteine, D = aspartic acid, E = glutamic acid, F = phenylalanine, G = glycine, H = histidine, I = isoleucine, K = lysine, L = leucine, M = methionine, N = asparagine, P = proline, Q = glutamine, R = arginine, S = serine, T = threonine, V = valine, W = tryptophan, Y = tyrosine. Adapted from Yamamoto et al. (1990). Reprinted with permission.

with the AB blood type are therefore universal recipients because this lack of antibodies means that other red blood cell antigens are not attacked when transfused.

Obviously, anybody can accept their own blood type because the donated red blood cells look the same as the recipient's. If the transfused red blood cells have different antigens on their cell surface, the recipient's antibodies that are present in the plasma will recognize them as foreign. A transfusion of the wrong blood type causes a strong immune response, resulting in the lysis of the transfused red blood cells, and even today – with all our modern medical technology – it is fatal to the recipient (Viel, 2009).

Many activities have been published that guide students in constructing models of the different ABO antigens, and in simulating the transfusion compatibilities between different blood types (Sharp & Smailes, 1989; Arico, 1995; Wake, 2005).

○ The Molecular Basis of ABO Genes

The A and B transferases are both proteins, and each is 354 amino acids long. They differ from each other by four amino acids, as shown in Figure 3. They are coded for by genes that differ by seven base pairs, four of which result in the observed amino acid changes (Yamamoto et al., 1990). The O gene is another story. It differs from the A gene by a single-base deletion at nucleotide position 258. This single-base deletion is a frameshift mutation. As a result, the protein coded for by the O gene is only 117 amino acids long, and every amino acid after amino acid number 88 is incorrect, as shown in Figure 3. This resulting truncated protein has no enzymatic activity.

○ The ABO Blood Group Is an Example of Multiple Alleles

Multiple alleles occur when there are more than two possible alleles for a single chromosomal locus. The ABO blood group is a classic example of this. Every person has two number 9 chromosomes and, therefore, two alleles for ABO blood types. However, there are three possible alleles—I^A, I^B, and i (Type O)—that can occur on each number 9 chromosome. Thus, people will have two of these three possible alleles. A single person will have either two of the same allele or two different alleles, in any combination.

○ A Possible Evolutionary Advantage to Having More Than One Blood Type

Why do people have more than one blood type? Berg et al. (2007) suggested a possible evolutionary advantage to having more than one blood type in a population. If some pathogen had an oligosaccharide on its surface that was similar to the oligosaccharide associated with one of the ABO blood groups, people with that blood type would not be likely to mount a vigorous immune response to that pathogen, since it looked like "self." They would therefore be susceptible to that pathogen, whereas people with a different blood type would be less susceptible and, therefore, more likely to survive such an infection. Having different blood types is thereby an inherited variation that makes it more likely that some members of a population will survive a particular epidemic.

○ Acknowledgments

Thanks to Alain Viel for his October 7, 2009, lecture on red blood cells. Special thanks to Harvard University's Life Sciences–HHMI Outreach Program for sponsoring this lecture and many others that have greatly enriched classroom teaching. Thanks to Jacqueline Brooks for helpful conversations. Thanks to Nadav Kupiec for expert preparation of the artwork.

References

Arico, A. (1995). Blood type compatibility: a simulation of medical transfusion reactions. *American Biology Teacher, 57,* 108–110.

Berg, J.M., Tymoczko, J.L. & Stryer, L. (2007). *Biochemistry, 6th Ed.* (p. 315). New York, NY: W.H. Freeman.

Landsteiner, K. (1900). Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe. *Zentralblatt Bakteriologie, 27,* 357–362.

National Center for Biotechnology Information. NCBI databases. http://www.ncbi.nlm.nih.gov.

Sharp, J.D. & Smailes, D.L. (1989). A simulation of the blood type test. *American Biology Teacher, 51,* 232–233.

Viel, A. (2009). Structure and physiology of red blood cells. [Lecture, October 7, 2009, as part of Harvard University's Life Sciences–HHMI Outreach Program.]

Wake, C. (2005). ABO/Rh blood-typing model: a problem-solving activity. *American Biology Teacher, 67,* 158–162.

Xu, R., de Vries, R.P., Zhu, X., Ncyholat, C.M., McBride, R., Yu, W., Paulson, J.C. & Wilson, I.A. (2013). Preferential recognition of avian-like receptors in human influenza A H7N9 viruses. *Science, 342,* 1230–1235.

Yamamoto, F., Clausen, H., White, T., Marken, J. & Hakomori, S. (1990). Molecular genetic basis of the histo-blood group ABO system. *Nature, 345,* 229–233.

SUSAN OFFNER is a biology teacher at Lexington High School, 251 Waltham St., Lexington, MA 02421; e-mail: soffner@ix.netcom.com.

Appendix: Oligosaccharides & Their Relationship to the Glycocalyx

What Oligosaccharides Are

Chemically, oligosaccharides are some monosaccharides joined by covalent bonds. There are typically between 4 and 15 monosaccharides in an oligosaccharide. And while some of the monosaccharides in oligosaccharides are nice, well-behaved sugars (glucose or galactose, for example), many of the monosaccharides are unusual. Some contain nitrogen (N-acetylglucosamine or N-acetylgalactosamine), others might have methyl groups on their terminal carbon atom (fucose), and others are unusual in other ways.

Where Oligosaccharides Are Located

The oligosaccharides we discuss here are located on the outside of the cell membrane, in a structure called the *glycocalyx*. They can be attached to proteins (glycoproteins) or to lipids (glycolipids = glycerol plus two fatty acids plus an oligosaccharide). Oligosaccharides are not found on the inside of the cell membrane.

Why Oligosaccharides Are Important

Oligosaccharides are an important part of what the immune system recognizes. Early in development, your immune system learns to recognize the oligosaccharides on the outside of your cells and identify them as "self." It will not mount an immune response to these oligosaccharides. However, later in life, if the immune system encounters an oligosaccharide that it does not recognize as "self," it will mount an immune response to it.

Oligosaccharides are also important because they can serve as receptors for the attachment of viruses. Viruses need to attach to a receptor on the cell membrane in order to be able to infect a cell. Very often, the receptor a virus recognizes is an oligosaccharide on the outside of the cell membrane. For example, the receptor for the flu virus is an oligosaccharide. Typically, these oligosaccharides have other functions in the cell. The cell becomes vulnerable to a viral infection when a virus evolves that can recognize and attach to one of these oligosaccharides. In order to do this, the proteins on the surface of the virus have to be complementary in shape and charge to the oligosaccharide to which they bind.

Why Oligosaccharides Are Inherited

Monosaccharides, of course, are not inherited. Genes are. However, each monosaccharide in an oligosaccharide is added to the oligosaccharide by an enzyme. These enzymes are proteins that are coded for by genes. Therefore, the particular oligosaccharides that will be on the outside of your cells are determined by your genes. In some cases, all people share a particular oligosaccharide because we all have the genes to construct that oligosaccharide. An example is the flu virus receptor, which, as far as we know, is found in all people. It is different from the flu virus receptor in birds because birds have different genes than we do, so they make a different oligosaccharide (Xu et al., 2013).