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Genetic of the ABO blood system and its link with the immune system

A genética do sistema ABO e sua relação com o sistema imune

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*In the book "Eat Right For Your Type" the author Peter J. D'Adamo writes that the O blood type was the first blood type to appear in humans and affirms that the blood groups are the key to the immune system. Some recent phylogenetic network studies in humans and non-human primates implies that the A gene represents an ancient form of the ABO genes. Relationships between blood groups and infectious and noninfectious diseases and immunodeficiency abnormalities have also been reported in the literature. As D'Adamo's propositions seem to be in opposition with the current knowledge, we present in this paper some comments about the genetics and the evolution of the ABO blood group genes and some links between this blood system and the functioning of the immune system. Rev. bras. hematol. hemoter. 2004;**26** (1):60-63.*

Key words: *ABO system; genetics; polymorphism; immune system*

Introduction

In 1997 the American naturopathic physician Peter J. D'Adamo wrote a book entitled "Eat Right For Your Type" in which he presents a dietary program based on the ABO blood types.[1] Also, the author explores some aspects of the genetics and the evolution of this blood system and affirms that the blood groups are the key to the functioning of the immune system. It is not our intention to discuss here the supposed links among ABO blood types to any dietary program. Instead, we wish to present some comments about two questions related to the genetics and evolution of the ABO blood group genes and the links between this blood system and the immune system according to current knowledge, which are different to D'Adamo's propositions.

Was the O type the first blood type to appear in humans?

Dr. D' Adamo writes that the O blood type of the ABO blood system was the first human blood type. The ABO blood group system is a genetic trait determined by genes occupying the ABO locus on chromosome 9 (9q34.1). This blood system is characterized by the expression of two carbohydrate antigens (A and B) expressed on the red blood cell membrane and in many other tissues and two plasmatic antibodies (anti-A and anti-B) that appear after birth. The synthesis of these antigens is controlled by specific glycosyltransferases. The *A* and *B* genes code to functional glycosyltransferases capable of converting the H antigen precursor into A or B antigens. The *O* gene codes to an anomalous glycosyltransferase that is incapable of modifying the H

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antigen. Independently, the synthesis of the red blood cell H antigen is controlled by an a-2-L-fucosyltranferase coded by the *H* gene (FUT-1) of the locus H located in the chromosome 19 (19q13.3), from the precursor type 2 oligosaccharides (Galb1®4GluNAc). In individuals with the secretor phenotype, the *SE* gene (FUT-2) codes to a similar a-2-L-fucosyltransferase that is capable of synthesizing the H antigen from the precursor of the type 1 oligosaccharide (Galb1®3GluNAc) in other tissues.[2] Therefore, the *A*, *B*, *H* and *SE* genes code to functional glycosyltransferases but the *O*, *h* and *se* genes are incapable of this.

In order to agree with the assertion that the O blood type was the first human blood type to appear, it would be necessary to admit that before humans, only the H locus existed in non-human primates, but this does not make any sense. Many papers were able to demonstrate the presence of ABO antigens and the glycosyltransferases responsible for the synthesis of the A antigen in tissues and secretions collected from other non-human primates.[3,4,5] Another possibility would be to accept that the *O* gene evolved before the *A* and *B* genes in the ABO locus. After constructing phylogenetic networks of human and non-human ABO alleles, Saitou and Yamamoto concluded that the *A* gene represents the ancestral form.[6] Thus, in the evolutionary sense, it is difficult to believe that normal genes like *A* and *B* have evolved from abnormal genes like *O*.

The three most common *O* genes identified in different populations are O^1, O^{1v} (variant) and O^2.[7-11] Compared to the ancestral form, the O^1 and O^{1v} genes have a deletion of a G base in exon 6 (guanine in position 261) and show additional nucleotide differences.[10] The O^2 gene does not have the G deletion but has a substitution (G802A) in exon 7, which appears to abolish its function.[8,9] Although the O blood type is common in all populations around the world,[12] there is no evidence that the *O* gene represents the ancestral gene at the ABO locus. Nor is it reasonable to suppose that a defective gene would arise spontaneously and then evolve into normal genes.

Is the ABO blood system the key of the immune system?

Dr. D'Adamo also asserts that the ABO blood group system is the key to immune function. There are interesting interactions among blood types and the immune system. The blood types are characterized by polymorphic antigens expressed in the red blood cell outer membranes and in other tissues, similar to ABO.[2,13] Due to immunogenicity, blood group antigens induce immune responses following incompatible transfusions, during pregnancy or after organ transplantation. Environmental stimuli also contribute to the production of so-called "natural antibodies". Thus, a person can produce regular and irregular antibodies specific to blood group antigens. This feature represents a link between the blood groups and immune function but is not the key to the immune system.[2]

The biological functions of blood group polymorphisms are not completely understood but many blood group antigens act as important molecules in the cell-cell recognition involved in early embryonic tissue differentiation and probably as a self declaration mechanism in somatic cell communities.[2,14]

There is also abundant evidence that blood groups play a role in the susceptibility or resistance to various infectious and non-infectious diseases.[15] One of the arguments used to reinforce the role of these molecules is the higher expression of the ABO carbohydrates in secretions and tissues that have contact with the environment such as in the skin and in mucous membranes of respiratory and gastrointestinal tracts.[2] As infectious processes are related to the attachment of microbes to molecules expressed in host cells, probably the ABO (and its associated genetic systems, Secretor and Lewis) carbohydrate antigens evolved to create a polymorphic profile in the mucous membrane. This is important to alter potential receptors of bacteria, viruses, etc.[16] Therefore, diversity of these antigens can be related to the susceptibility or resistance to infectious diseases and this feature also represents a functional relationship between blood groups and the immune function. Experimental evidence demonstrated the importance of the H antigen, expressed in gastric mucous membrane, to the attachment of *Helicobacter pylori* bacillus.[17,18] Some epidemiological studies observed that the O blood group is more common among individuals infected by this pathogen.[19,20,21] Other papers also suggested that similar mechanisms are implied in susceptibility of the Lewis negative phenotype [Le(a-b-)] to the uro-pathogenic *Escherichia coli* strain.[22,23,24] Despite these facts it is difficult to believe that blood types represent the key to the immune system. It is worthwhile remembering that a small number of blood group systems express their antigens in tissues other than hematopoietic tissue.

Rare *null phenotypes* were described in many blood systems, some of which are associated with diseases, but this is not a general rule. For example, carriers of McLeod phenotype have a weak expression of Kell antigens and do not express the Kx substance in their red blood cell membrane. However, some phenotypes have an immune dysfunction named X-linked chronic granulomatous disease.[25] Carriers of Rh null syndrome, a hematological disorder characterized by mild or moderate hemolytic anemia, do not express Rh antigens in the red blood cell membrane but this phenomenon is not related to immune dysfunction.[26] Besides there is no evidence of any immune

dysfunction among carriers of the Bombay phenotype, a rare phenotype in which the A, B and H antigens are absent, but the anti-A, anti-B and anti-H are expressed.[2]

The immune system is a biological system that evolved to discriminate self from non-self using a complex network of T and B lymphocytes, antigen presenting cells, cytokines, antigen receptors, antibodies, MHC restriction and other cellular and molecular interactions. They is important due to their ability to protect us against intracellular and extra-cellular pathogenic micro-organisms through cellular and humoral immune responses.[27]

Although there are links between the immune system and blood group phenotypes, antibodies are produced by the cells of the immune system and not by the blood type loci. It is possible to detect the A and B antigens in red blood cells and in secretions of newborn babies but they do not express anti-A and anti-B antibodies until several months of age. Possibly the influence of environmental stimuli resulting from similar carbohydrates expressed in microorganisms contributes to the production of natural antibodies.[2,27] It is also worthwhile to note that in the ABO blood group system, the only system in which "regular antibodies" can be detected, the specificities of anti-A, anti-B and anti-A,B are necessary, but not sufficient to protect the body against the higher antigen diversity present in the environment and for normal immune function. Of course, the blood type antigens and their specific antibodies are part of but certainly not the key to the immune system.

Concluding remarks

The A, B, H and precursor oligosaccharides in many mammalian species, in humans and non-human primates as well as the glycosyltransferases responsible for their synthesis have been well characterized at the biochemical and molecular levels. The resulting knowledge can help not only in the definition of an appropriated model to explain the evolution and the biological importance of the ABO blood system related to diseases, but also to repudiate any absurd speculation without scientific base. Finally, the complexities of the blood types and their relationship with the functional aspects of the immune system deserve much additional study. In the meantime, D'Adamo's speculations about the evolution of the ABO blood types and the blood groups as the key to the immune system appear to be fundamentally flawed.

Resumo

Peter J. D'Adamo, autor do livro "Eat Right For Your Type", escreve que o grupo O representa o primeiro tipo sangüíneo que surgiu nos humanos e também afirma que os grupos sangüíneos constituem as bases do sistema imune. Recentes estudos filogenéticos realizados em primatas humanos e não humanos estabeleceram que o gene A representa a forma ancestral dos genes que ocupam o locus *ABO. Associações entre os grupos sangüíneos ABO, doenças infecciosas, não infecciosas e imunodeficiências também foram relatadas. Diante das proposições do autor, as quais se opõem às informações resultantes de recentes estudos moleculares e filogenéticos, nossa intenção é apresentar algumas reflexões sobre a genética e a evolução dos genes do sistema ABO e as conexões deste sistema com o sistema imune. Rev. bras. hematol. hemoter. 2004;**26** (1):60-63.*

Palavras-chave: *Sistema ABO; genes ABO; sistema imune*

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