Molecular polymorphisms of human blood groups: a universe to unravel

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The discovery of the ABO blood group system by Karl Landsteiner in 1900 resulted in the description of the first human genetic polymorphism and the birth of Immunohematology.[1] In the decades that followed, new blood group systems were characterized and the frequencies of their common and rare phenotypes were established in almost all populations and ethnic groups.[2]

Immunohematology takes advantage of red blood cell agglutination methods to demonstrate the extensive phenotypic polymorphisms of these systems and explain their patterns of Mendelian inheritance. The development of new serological methods and reagents reached its peak with the introduction of automation in immunohematology.[3] The resulting advances have clearly established the importance of these polymorphic systems in transfusion medicine, in the genesis of newborn hemolytic diseases, in autoimmune anemia and, in some cases, in solid organ transplantation.[4] The immunohematology methods broke barriers and are even being used in other areas, such as to understand and teach genetics, biochemistry and immunology.

In recent years, immunohematology has been experiencing technological advances in the molecular characterization of blood group system polymorphisms. The genes that control the expression of blood group antigens have been cloned and sequenced and the molecular basis of their polymorphisms identified.[5] These advances have improved the classification of genotypes and phenotypes of blood groups in patients who recently received transfusions, who have positive direct Coombs tests and, in some situations, where rare sera are not available. Moreover, they have allowed the determination of fetal Rh status from maternal blood plasma and the investigation of atypical inheritance patterns that are unexplainable by classical Mendelian genetics.[6,7]

In this issue of the Journal of Hematology and Hemotherapy, Visentainer et al. present the results of a pioneer molecular evaluation of the polymorphisms of the Rh, Kell, Duffy and Kidd blood group systems in volunteer blood donors and candidate bone marrow donors of both genders from northwestern Paraná State, Brazil. The authors used conventional and molecular methods to define common and rare allele frequencies. They demonstrated that the observed genotypic proportions did not deviate from those expected for populations that comply with the principles of the theorem of Hardy-Weinberg equilibrium. They compared their results to those reported in the State of São Paulo and stressed that the differences found for the Rh, Duffy and Kidd systems result from the distinct predominance of European ancestry in southern Brazil. The results reflect the careful selection of casuistic and the choice of methods to assess molecular polymorphisms.

The range of phenotypes in humans are a direct result of genetic variations which act together with environmental and behavioral factors to produce diversity.[8] Based on the population impact, genetic polymorphisms can be grouped as two types: transient and balanced. A transition polymorphism has a restricted distribution, occurs at low frequencies and as it does not seem to offer advantage to carriers, gradually tends to become extinct. On the other hand, a balanced polymorphism, as it offers an apparent selective advantage, tends to gradually increase in frequency in populations.[9] Both types of polymorphisms are present in genes that control the blood group antigen expression.[10]

The identification of gene polymorphisms, which control the blood group antigen expression, contributes to the understanding of the biological significance of blood group systems. In addition to assisting in the characterization of allelic variations, the identification of gene polymorphisms allows us to estimate the processes involved in the formation of different populations (the founder effect, genetic drift, migration, etc.). Thus, blood group gene polymorphisms are valuable predictors of genomic ethnic ancestry.[8,10]

Population studies are often used to investigate the biological significance of blood group polymorphisms in respect to susceptibility to disease and other pathophysiological conditions. Results from these investigations provide additional data for clinical analysis

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and preventive and therapeutic measures. The association between maternal immunization and newborn hemolytic diseases as well as resistance to malaria caused by *Plasmodium vivax* observed in carriers of the Duffy negative phenotype [Fy(a-b-)] illustrate these conditions.[11]

The molecular basis of blood group polymorphisms is well understood. However, environmental factors that contribute to the appearance of polymorphisms are still unclear. The absence of polymorphisms in some blood group genes suggests that the maintenance of conserved sequences is important but not indispensable from the biological point of view. For example, the *FUT1* gene (19q13.3) that controls the expression of the H type 2 antigen in hematopoietic tissue is monomorphic, but its absence in the Bombay phenotype appears to offer no biological disadvantage. In contrast, the variability observed in other genes, for example, the *FUT2* gene (19q13.3) supports the concept that blood group polymorphisms in the population are maintained by balanced selection mechanisms. However, the bases of this form of selection are still unknown.[10,12]

Studies such as the one by Visentainer et al. are aligned to the contemporary interest in understanding the significance of polymorphisms in biological systems and populations and contribute to elucidate the results of evolutionary pressure that created and maintain genetic, genotypic and phenotypic variability of human blood group systems. The gene polymorphisms of the human blood groups are very diverse and are an attractive research field. This is a universe to be unraveled.

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