

Technical Monograph No. 6

The Rh Blood Group System

History

It was Landsteiner and Wiener ¹ in 1940 who originally described the Rh system. They injected the red cells of the Rhesus monkey into rabbits (and later guinea pigs) and produced an antibody which not only agglutinated Rhesus monkey red cells but also the red cells of approximately 85% of New York white people. The people who reacted apparently possessed an antigen similar to the Rhesus monkey and were called Rhesus positive. The remainder whose cells did not react were called Rhesus negative. The antigen was called D and the antibody anti-D. Examples of human produced immune antibodies were also found, which were shown to react in a similar manner to the animal produced antibody, i.e. with the red cells of approximately four out of five people. It has subsequently been shown that the antigens detected by these different antibodies belong to two different blood group systems. The blood group system described by the human derived antibodies is now termed Rh, whereas the system originally described by Landsteiner and Wiener is now termed LW. The two systems are now able to be differentiated serologically, biochemically and genetically. The genetic locus for Rh is known to be linked to the gene for elliptocytosis ² (ELI) and is on the short arm of chromosome 1 in the region p36.2-p34.

The study of other subsequent Rh antibodies produced in humans, revealed that many contained more than one antibody specificity, which led to the discovery of the other Rh antigens C, c, E and e. The Rh Blood group system is the most polymorphic of the human blood groups, consisting of at least 45 independent antigens and next to ABO is the most clinically significant system in transfusion medicine.

Rh Genetics

Two rival theories have developed over time. Each theory has attempted to explain Rh genetics and inheritance. Wiener ³ (USA) proposed a single gene locus theory that involves the use of a complex Rh-Hr notation. This was able to accommodate some of the observed genetic variations but it has been difficult to understand and apply at a practical level.

Fisher and Race ⁴ (UK) proposed a three-gene locus theory. Their system uses a CDE nomenclature, which although very limited in its ability to accommodate some of the genetic and serological variations that have subsequently been described, has the advantage of being much easier to understand and is easily applied at a practical level.

In contradiction to the one and three gene models, DNA studies have shown that there are in fact only two Rh genes, one coding for D and the other for CE. A related protein, the Rh glycoprotein (RhAG) is essential for the assembly of the Rh protein complex in the erythrocyte membrane and for the expression of Rh antigens. The two Rh genes produce two protein products, D and CcEe. Therefore, a person who is RhD positive would have two genes, one coding for D, the other for the C or c and E or e antigens⁵ (i.e. as Ce, ce, CE or cE). A RhD negative individual lacks the D gene and therefore does not produce the D polypeptide in their red cells (producing only the CE protein). This explains why no allele to the D antigen (i.e. d) has been described. The absence of the D polypeptide in RhD negative people does not appear to be associated with any red cell membrane dysfunction, but does provide an explanation as to why the D antigen is so immunogenic to RhD negative people. Many unusual Rh variant types have been described and these are attributed to a variety of genetic causes (e.g. mutation, unequal crossing-over, gene conversion, etc.), involving the two gene loci. However, even though cloning of the Rh genes by molecular genetics indicates a two gene model for Rh, the three gene model originally proposed by Fisher-Race in 1944, remains useful at a practical level for describing what is encountered.



Rh Nomenclature and Inheritance

The complexities of the multi-allelic Rh blood group system have been simplified by the International Society of Blood Transfusion and a slightly modified numerical notation from the one developed by Rosenfield et al ⁶ has been adopted. This nomenclature comprises 45 Rh antigens that are numbered RH1 to RH51 with six antigens obsolete. The most important of these is RH1, which is the D antigen.

A basic explanation of the principles of the Fisher-Race nomenclature is required because of the close linkage of the Rh gene combinations in their model. The Rh gene combinations in the Fisher-Race model are inherited through successive generations as a unit (i.e. crossing over between gene triplets is a very rare event). The triplet of genes therefore behaves as though it is a simple Mendelian dominant character. Eight (haplotype) gene complexes are possible from the three CDE loci model, each of which has been given a 'shorthand' notation. The use of 'R' indicates the presence of the D gene, whereas the use of 'r' indicates its absence (i.e. d).

The D Antigen

It was Stratton ⁷ in 1949 who first used the term D^u for a D antigen that was only detected by some anti-D reagents. It was this discovery that prompted the use of different anti-D reagents. The definition of D^u evolved to become the D type of those red cells which are not directly agglutinated by IgM anti-D, but which react with IgG anti-D in the antiglobulin test. This is a test in which red blood cells are incubated in serum, washed to remove free immunoglobulins, and then exposed to an antiglobulin reagent that is formulated to detect the cell-bound IgG. Although the incidence of D^u is highest among the Negro races, it also occurs in about 1% of the population in the UK. There is no qualitative difference between D^u and D; they differ ONLY in the number of antigen sites present on the surface of each red cell. The term D^u should be discontinued and the term 'weak D' used instead.

The D antigen is highly immunogenic and induces an immune response in 80% of D-negative people transfused with 200 ml of D-positive blood ⁸. In most countries D typing is done on both donor and recipient to avoid this immunisation problem. Approximately 95% of black Africans are D positive and it reaches almost 100% in some populations in the Far East. The Rh genes appear to be a source of massive diversity, and combinations of all these different genetic arrangements abound among all racial groups. It is beyond the scope of this monograph to discuss each and all of these variations and the reader is referred to more detailed literature ⁸.

Haemolytic Disease of the Newborn

In 1939 Levine and Stetson ⁹ demonstrated that maternal antibodies crossing the placenta could damage foetal red cells possessing the antigen specific for the maternal antibody. This results in a condition known as Haemolytic Disease of the Newborn (HDN). Since only IgG antibodies are capable of crossing the placenta (IgM antibodies are too large), it is these antibodies when active at 37°C which can cause HDN, and almost all specificities of these antibodies have been implicated. However, in the majority of cases the causative antibody is anti-D, the mother being RhD negative and the foetus having inherited a D antigen from the father. The first child is seldom affected by HDN since the stimulation of the antibody is frequently due to a transplacental haemorrhage from the foetus to the mother during delivery. A large number of cases of HDN due to anti-D can be prevented by giving an injection of a potent anti-D immunoglobulin to the Rhesus negative women bearing a Rhesus D positive child.

If given within 72 hours of delivery, the anti-D is able to destroy any RhD positive foetal cells before they reach the sites of antibody production. Current guidelines recommend the administration of at least 500iu to all non-sensitised RhD negative women at 28 and 34 weeks and post-natally if the baby is RhD positive. The D antigen accounts for approximately 50% of all cases of HDN; the remainder is due to K, c, C/G, E and Fy^a. Foeto-maternal Rh incompatibility still represents a major cause of HDN. Foetuses who are R₂ usually have a more severe anaemia than their R₁ counterparts. There is also evidence that male foetuses have a more severe HDN than female foetuses ¹⁰.

Considerable progress has been made in the understanding of the molecular basis of Rh and other blood group antigens in the past ten years. The function of the Rh complex is still not clear. It is known that some correlation exists between the Rh complex and ammonium transport and it could cotransport with other cations. The Rh complex is a major red cell protein of considerable clinical importance but our understanding of its functionality in human red cells still relies on circumstantial evidence.



References

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