The Human RhD Protein and Hemolytic Disease of the Newborn

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Abstract

Hemolytic disease of the newborn (HDN) occurs during pregnancy when the red blood cells of an RhD positive (RhD+) baby comes in contact with the immune system of an RhD negative (RhD-) mother. The mother's immune system identifies the RhD protein on the baby's erythrocytes as foreign, and produces anti-D antibodies which cross the placenta causing destruction of the baby's red cells. Resulting symptoms range from mild jaundice and anemia to perinatal death. The RhD protein belongs to an ancient family of ammonia channels and is found on RhD+ erythrocytes but is missing from RhD- red cells. The St. Dominic S.M.A.R.T. Team has modeled RhD using 3-D printing technology. Our model highlights RhD's twelve transmembrane helices and the sidechains of its nonfunctional ammonia channel. Extracellular loops 3, 4, and 6 carry clusters of D antigen epitopes while loops 1, 2, and 5 do not play a major role in RhD antigenicity due to their sequence identity with RhCE. The RHD gene arose from gene duplication of the RHCE gene and has 93.8% homology. Along with RhAG (Rh associated glycoprotein) both RhD and RhCE are part of the trimeric Rh complex on erythrocytes, essential to the cell's structural integrity. HDN research led to the discovery of RhD and to the highly complex Rh blood group system whose major antigens are D, C/c, and E/e. Hemolytic disease of the newborn is now preventable by injecting RhD- mothers with Rh immune globulin to prevent them from developing active immunity to their babies RhD+ erythrocytes.

RhD Positive and RhD Negative

The RhD protein is found in the cell membranes of red blood cells. People who have this protein are considered RhD positive (RhD+), and people who lack this protein are considered RhD negative (RhD-).

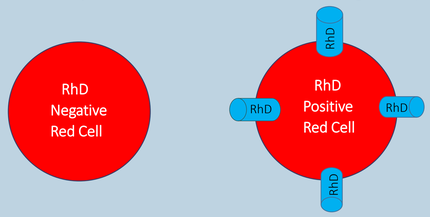

Figure 1: RhD- and RhD+ Red Blood Cells

Hemolytic Disease of the Newborn

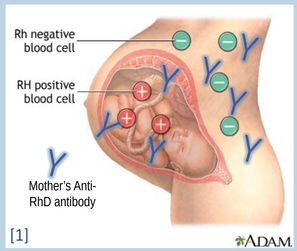

Figure 2: Mother's anti-RhD Antibodies Cross the Placenta

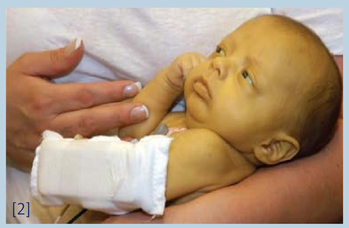

Figure 3: HDN Baby with Jaundice

Hemolytic disease of the newborn (HDN) occurs during pregnancy when the red blood cells of an RhD positive (RhD+) baby cross the placenta and come in contact with the immune system of an RhD negative (RhD-) mother. The mother's immune system identifies the RhD protein on the baby's red cells as foreign, and produces anti-D antibodies (blue in Figure 2). The antibodies cross the placenta and tag the babies red blood cells to be destroyed by macrophages. When the red blood cells are destroyed, the breakdown of hemoglobin causes a bilirubin buildup in the bloodstream, giving the baby a jaundiced, or yellow coloring. The baby becomes anemic and the bilirubin overload can cause can cause brain damage, many physical abnormalities and even death.

Structure of the RhD Protein

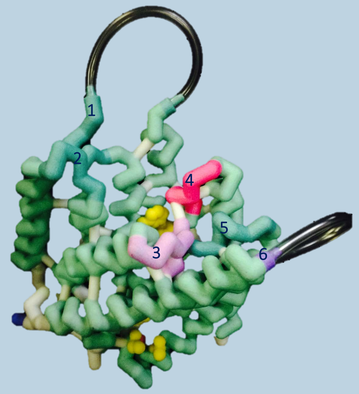

Figure 4: Extracellular view of RhD

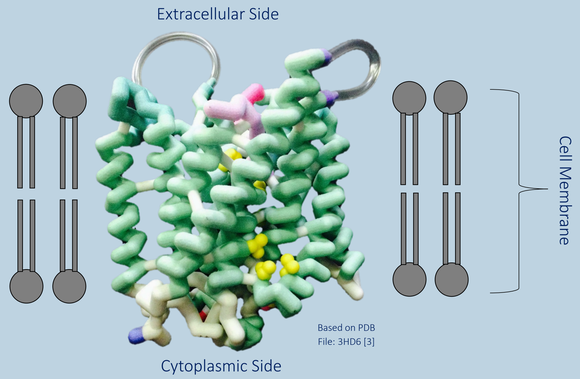

Figure 5: RhD in the Red Blood Cell Membrane

The human RhD protein belongs to an ancient family of ammonia channels and is found on RhD+ red blood cells; it is missing from RhD- red cells. RhD has 12 transmembrane helices (green) and a nonfunctional ammonia channel (yellow). Extracellular loops 3, 4, and 6 (Figure 4) carry D antigen epitopes important in blood typing and hemolytic disease of the newborn. Loops 1,2 and 5 are not usually antigenic because of their sequence identity with the RhCE protein. The RhCE protein is also found on red bloods cells and differs from RhD by only 32-35/416 amino acids. [3] [4] [5]

RhD and RhCE Genetics

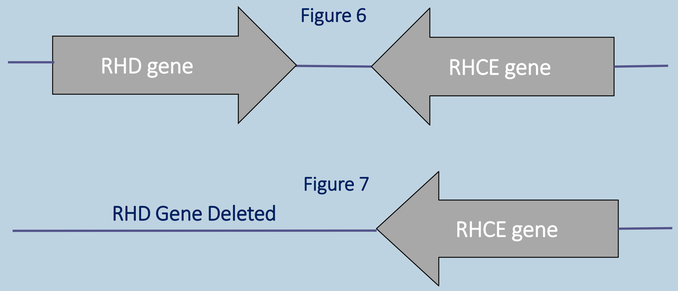

Figure 6: Positions of RHD and RHCE Genes on Chromosome One
Figure 7: RHD Gene Deletion in Caucasians

During evolution, the RHD gene arose from the RHCE gene by duplication. The two genes are located next to each other on the chromosome 1 (Figure 6) and are 97% identical. [3] [4] Their positioning facilitates recombination to produce multiple Rh alleles, increasing this blood group's complexity. A complete deletion of the RHD gene occurs in 15-17% of Caucasians and these individuals are at risk for hemolytic disease of the newborn.

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Preventing HDN with RhD Immune Globulin

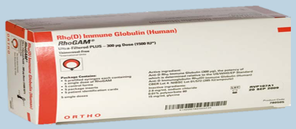

Figure 9: RhoGAM was the first commercial source of Rh immune globulin.

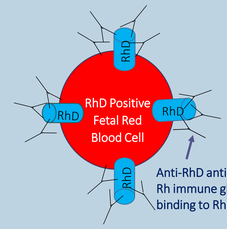

Figure 10: Rh immune globulin makes RhD+ red cells non antigenic.

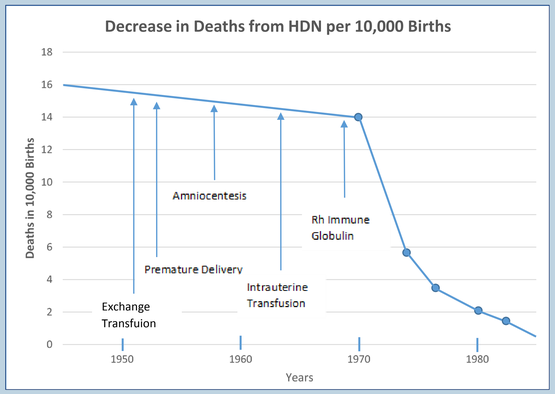

Figure 11: Decrease in Deaths from HDN as Clinical Management Improved [8]

Intensive research into prevention of HDN with Rh immune globulin occurred in the 1960s. First, it was demonstrated that red blood cells covered with anti-RhD antibodies from Rh immune globulin were not antigenic.[7] Successful large scale clinical trials were carried out in several countries, giving Rh immune globulin to mothers at delivery.[8] In 1965, Zipursky demonstrated that Rh immune globulin could be given to the mother before birth without harming her fetus.[9] The antibodies coated any RhD+ fetal red blood cells entering the mother's circulation to prevent the mother's immunization (Figure 9). Today, Rh immune globulin is given at 28 weeks. Figures 11 shows the dramatic effectiveness of Rh immune globulin in the treatment hemolytic disease of the newborn.

Conclusions

The RhD protein belongs to one of the most complex blood group systems, the Rh system. In transfusion medicine, it is second in importance only to the ABO system. In the past, RhD+ babies of RhD- mothers often became ill or died when the mother's antibodies to RhD crossed the placenta and targeted fetal red blood cells. The discovery that Rh immune globulin given to the mother prevents the development of active immunity has revolutionized the prevention and treatment of hemolytic disease of the newborn.

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