

# Clearance mechanisms of incompatible red blood cells essay sample

[Technology](#), [Development](#)



The binding of antibodies to red blood cells can lead to potentially fatal outcomes such as hemolytic transfusion reactions, autoimmune hemolytic anemia, and hemolytic disease of the fetus/newborn. 1 Information regarding the first steps of hemolytic transfusion reactions is well documented. It is, however, unclear why the severity of hemolytic transfusions experienced by different individuals ranges from mild to very severe. 2 The pathophysiology of the final pathways and downstream events of red blood cell hemolysis are also yet to be fully elucidated although research is ongoing. 2 A recent study by Liepkalns et al. (2012)<sup>1</sup> has reinvigorated debate on the clearance of incompatible RBCs from the bloodstream. The findings of this study seem to implicate additional mechanisms (other than the currently known mechanisms) in the clearance of foreign incompatible red cells. This paper will review the currently known mechanisms for removal of incompatible red blood cells from the circulation.

## **Red Blood Cell Clearance Mechanisms**

Incompatible red blood cells can be cleared from the circulation through two main mechanisms: intravascular and extravascular (reticuloendothelial) clearance. 3 Both mechanisms are mediated by the immune system. 4 Intravascular mechanism is the mechanism through which incompatible foreign red blood cells are destroyed within the bloodstream and their hemoglobin released into the circulation. 1 This type of reaction is caused by either IgG anti-A or anti-B or IgM antibodies. These antibodies rapidly activate the complement cascade often via the classical pathway. 3, 4 The binding of antigens to a minimum of 2 IgM antibody binding sites can lead to the activation of the complement cascade. 3, 4 For IgG molecules to activate

the complement cascade, 2 of the molecules must attach in close proximity to one another on the membranes of red blood cells to form a doublet. 3 The coating of red blood cells with a complement activating antibody results in the formation of antigen-antibody complexes that activate C1, the first component of the complement system. Sequential progression of the activated complement cascade to the C5b-C9 lytic complex leads to defects in the membranes of the red cell. These defects permit entry of ions into the red cell which finally swells and ruptures releasing hemoglobin into the circulation. The released hemoglobin combines with plasma protein haptoglobin forming a complex. This complex is cleared from circulation by the mononuclear phagocyte system. Excess hemoglobin (i. e. that which is not bound to haptoglobin) is excreted in urine. 3 Some antibodies, on the other hand, simply adhere to donor red blood cells causing them to agglutinate. Agglutinated cells can either survive or are cleared from circulation prematurely by macrophages. 4 Notably, activation of the complement system by the binding of recipient antibodies to donor red cells in sensitized patients leads to the lysis of donor red cells and immediate intravascular hemolysis. Hemolytic transfusion reactions characterized by bleeding, disseminated intravascular coagulation, shock, renal failure, and death can then occur. 5 Of note is that IgM-mediated hemolytic transfusion reactions are potentially fatal while IgG-mediated transfusion reactions are less severe although they can also lead to death. 2

In the extravascular clearance system, intact incompatible red blood cells are cleared from circulation by cells belonging to the mononuclear phagocyte system found in the liver and spleen. Red blood cells sensitized

with complement up to the C3 stage or those coated with IgG that fail to progress to the C5b-C9 stage of the complement cascade interact with mononuclear phagocytes predominantly the macrophages. 3 Of note is that opsonization of red blood cells with antibodies does not automatically mean that the red cells are going to be destroyed. Rather, the rate of red blood cell destruction is influenced by the number of IgG molecules attached to a red cell as well as the number of antigens involved. 3 Macrophages attach to the Fc region of bound IgG1 and IgG3 molecules and C3b component of complement via their surface receptors. 2, 3 Once bound to the macrophages, sensitized red blood cells undergo distortion following which they may be engulfed by the macrophage. The engulfment maybe total or partial. Completely engulfed cells are destroyed inside the macrophage. The remaining parts of partially engulfed red cells continue circulating as spherocytes. The latter types of cells are more rigid than the normal red blood cells because of a loss of proteins and carbohydrates. This makes them prone to early destruction. Extravascular destruction of red blood cells leads to the release of hemoglobin breakdown products like bilirubin and urobilinogen into plasma and urine as opposed to free hemoglobin. The sites of removal of the red blood cells that are the liver and spleen may become enlarged. Jaundice may occur due to hyperbilirubinemia. Extravascular destruction of incompatible red blood cells can be prompted by IgG anti-D and other antibodies to Rh antigens. 3 This type of hemolysis can occur in utero when a sensitized RH negative woman is re-exposed to incompatible fetal red cells during subsequent pregnancies. The immune system of the mother makes IgG antibodies that are able to cross the placenta and bind to

fetal red blood cells. The IgG-coated fetal red cells are removed from circulation by the reticuloendothelial system (liver and spleen) of the fetus. 5

## **Origin of the Antibodies involved in the removal of Incompatible Red Blood Cells**

Incompatibility of red blood cells arises from the entry into circulation of foreign antigens that are antigens absent in the recipient's red blood cells prompting a reaction. 2, 4 This can occur as a result of pregnancy or blood transfusions. 4 Red blood cells usually contain antigens on the surface of their cell membranes. The antigens are protein or carbohydrate in nature. These molecules determine a person's blood group. The most clinically relevant blood groups are those belonging to the ABO and Rh blood grouping systems. Antibodies to the antigens of the ABO blood group develop naturally. Persons with antigens A, B, and AB on their red blood cells develop anti-B, anti-A, and no antibodies respectively. Patients with blood group O lack antigens on the surface of their red cells hence they develop both anti-A and anti-B antibodies. Antibodies against Rh antigens develop through immunization by incompatible red cells although some have been found to occur naturally. A first-time encounter with an Rh-Antigen by a Rh-negative person leads to a primary immune response. This response is characterized by a delay of several days with consequent production of the IgM antibody. This is followed by a switch to the production of IgG antibodies. IgM antibodies bind the triggering antigen weakly while IgG molecules are better targeted. The production of IgG continues long after the initial encounter providing life-long immunity. The first immune response also leads to the production of B cells also called memory cells. These cells enhance IgG

production during future encounters with the same antigen (secondary immune response). The latter response is much faster and better targeted. Production of the antibodies involved may remain high for many years. The memory cells may also undergo transformations to further enhance the way the antibodies they produce attach to antigens. 3

## **Antigen Processing during the Removal of Incompatible Red Cells**

The processing of antigens during the initial encounter entails engulfment of the antigen by a macrophage. The engulfed antigen is then digested and its antigenic fragments presented on the surface of the macrophages together with the major histocompatibility complex II (MHCII). A T-helper cell then binds to the combination of antigen/MCHII leading to interaction between the T-cell and the macrophage. The macrophage produces cytokines that stimulate the T-helper cell to secrete cytokines. The latter cytokines stimulate the growth and production of other T cells. 3 The activated T cell then departs to stimulate existing B cells to grow and divide to produce similar daughter cells. These daughter cells either become plasma cells or memory cells. Plasma cells elicit antibodies specific to the antigen that triggered their production. The role of memory cells is to produce antibodies during secondary immune responses. 3

## **Structure of Antibodies Involved in the Removal of Incompatible Red Blood Cells**

The most important antibodies in the clearance of incompatible blood cells are the IgG and IgM. 3, 4 All antibodies are immunoglobulins. They are made

up of 2 different polypeptide chains namely heavy (H) and light (L) chains. These chains are joined by disulfide bonds. IgG molecules can be broken down to 2 identical Fab fragments and 1 Fc fragment. Each of the Fab fragments has an antigen binding site. The Fc fragment has receptors for attachment to other cells such as macrophages, complement activation via the classical pathway, and placental tissue. IgG is a monomer while IgM is a pentamer. They constitute 70% and 10% of circulating immunoglobulins respectively. IgM has 10 antigen attachment sites and is very efficient at binding C1, the first component of the complement cascade. It is the latter process that leads to lysis of foreign red cells. 4

## **Conclusion**

In summary, incompatible red blood cells are cleared via two primary mechanisms that are the intravascular and extravascular clearance mechanisms. Both mechanisms are mediated by the immune system with macrophages, antibodies, and the complement system playing a major role in the recognition and processing of antigens and final lysis of the foreign blood cells.

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