Autoimmune hemolytic anemia: current understanding of pathophysiology

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A B S T R A C T

The autoimmune hemolytic anemias (AIHA) comprise a group of disorders characterized by hemolysis caused by antibodies directed against red blood cell (RBC) surface antigens. Based on the optimal temperature of antibody binding, AIHA is subdivided into 2 groups: warm type and cold type. Cold-type AIHA is further divided into cold agglutinin disease (CAD) and paroxysmal cold hemoglobinuria (PCH). Warm-type AIHA is the most common type of AIHA, in which IgG antibodies (Abs) are mainly directed against Rh antigens and RBC destruction takes place in the reticuloendothelial system. In CAD, the binding of IgM anti I/i antibody red blood cells at cold temperatures activates complement and results in intravascular hemolysis. PCH, the rarest of all types of AIHA, is a self-limited post-viral disease occurring mainly in children, in which specific IgG Abs bind RBCs at cold temperatures while complement activation occurs at body temperature. Drug-induced hemolytic anemia has recently been reclassified on the basis of the possible mechanisms involved. The basis for the immune dysregulation leading to the production of anti-red cell antibodies is still largely unknown, but recent studies have implicated several mechanisms of T-cell dysregulation with a decrease in T-regulatory cells and increase in pro-inflammatory Th17 cells. Progress in understanding the pathogenesis of AIHA may eventually lead to the development of more effective treatment.

Learning goals

At the completion of this activity, participants should be able to:
- understand the clinical and diagnostic features of warm- and cold-type autoimmune hemolytic anemia;
- comprehend the emerging immunological pathophysiology of autoimmune hemolytic anemias;
- understand the mechanisms involved in drug-induced autoimmune hemolytic anemias.

Introduction

The autoimmune hemolytic anemias (AIHA) constitute a group of uncommon disorders characterized by hemolysis caused by the formation of antibodies (Abs) directed against red cell surface antigens.[1] On the basis of the optimal temperature at which the auto-Abs bind to a patient's erythrocytes *in vivo,* immune hemolytic anemias are typically subdivided into 2 major groups: warm-type and cold-type. Cold-type AIHA is further classified into cold agglutinin disease (CAD) and paroxysmal cold hemoglobinuria (PCH). The term primary or idiopathic AIHA is applied when no recognizable underlying disease is present, whereas in secondary AIHA, the anemia is one manifestation of an associated disorder.

Although PCH is the least frequent type of AIHA, it was the first hemolytic anemia to be described at the end of the 19th century.[2] Its early recognition was due to the strikingly obvious symptom of hemoglobinuria and the fact that PCH was secondary to syphilis, a common disease at that time. Cold agglutinins were first described by Landsteiner in 1904.[3] Later, Banti *et al*. described the function of the reticuloendothelial system in red blood cell (RBC) hemolysis.[3] The distinction between congenital and acquired hemolytic anemia could not be made, however, until 1945, when Coombs and co-workers first showed the utility of the rabbit antihuman globulin test to determine the presence of RBC Abs in the serum of mothers whose newborns had Rh hemolytic disease (indirect Coombs).[4] They subsequently demonstrated that RBCs coated by non-agglutinating Rh Abs could be agglutinated by rabbit antihuman globulin serum.[1] This test, formerly known as Coombs test, is referred to as the direct anti-globulin test (DAT) and has since been recognized as essential for the diagnosis of AIHA.

AIHA is currently considered to be an organ-specific autoimmune disease in which RBCs are the target of the autoimmune recognition. However, the mechanisms initiating the abnormal production of RBC auto-Abs are still largely unknown.

The aim of this manuscript is to describe the current understanding of the different types of AIHA, as well as the associated immune dysregulation. The pathogenesis of drug-related autoimmune hemolytic anemia (DIHA) will also be discussed.

Warm-type autoimmune hemolytic anemia

Warm-type AIHA constitutes 70% of all

cases of AIHA. The annual incidence was calculated to be 1 per 75,000-80,000 persons.[2] The disease occurs both in children and in adults. Primary warm-type AIHA represents approximately 50-60% of reported cases, whereas secondary cases are associated with lymphoproliferative disorders, immune diseases, infections and, rarely, solid tumors.[2,5]

Pathogenesis

Rhesus (Rh) polypeptides are the most common targets for the pathogenic auto-Abs in patients with warm-type AIHA.[1] Other blood group antigens have been involved in a minority of patients, including protein 4.1, band 3 and others.[6-9] Several studies in humans have shown that Rh-like proteins are able to stimulate *in vitro* proliferation of mononuclear cells from peripheral blood or spleen samples of patients with AIHA but not of healthy subjects.[10,11] Interaction of the RBC with splenic macrophages may result in phagocytosis of the entire cell (Figure 1-1). More commonly, as the RBCs adhere to the macrophage via Fc receptors, part of the RBC membrane is internalized by the macrophage. This loss of membrane surface area results in the spherical shape of affected cells.

Clinical features

Common presenting complaints are weakness, pallor and jaundice resulting from the hemolytic anemia itself. Physical examination usually discloses modest splenomegaly in addition to the jaundice and pallor. Typically, the anemia is macrocytic due to the marked reticulocytosis. Blood smear often reveals the presence of polychromatophilia and spherocytes.

Laboratory diagnosis

The laboratory parameters indicating the presence of hemolysis include increased indirect bilirubin concentration, elevated serum lactate dehydrogenase level, and reduced serum haptoglobin level.[2,12] Screening of the patient's red cells using a polyspecific DAT reagent at 37°C reveals that the RBCs are coated with IgG auto-Abs, with or without complement (Table 1). These findings are sufficient for the diagnosis of warm-type AIHA. The selectivity of the antibodies eluted from the RBCs can then be determined using red cells lacking common blood group antigens.

Pathogenesis and therapeutic measures

As antibody-coated red cells trapped in the spleen are the cause of warm-type AIHA, potential therapeutic options are suppression of antibody production and splenectomy. Suppressing antibody formation can be achieved by steroid therapy, and anti CD20 and immunosuppressive therapy. The improved erythrocyte survival following steroid therapy probably results from a decrease in the synthesis of anti-RBC Abs.[13,14] However, the early improvement observed is probably associated with the reduced number of Fcγ receptors observed on blood monocytes during therapy.[13,15] Splenectomy and rituximab constitute second-line therapeutic options. Rituximab is a monoclonal Ab directed against B cells expressing CD20. The mechanism of action is the depletion of the B cells that produce antibodies against RBCs. The main beneficial effect of splenectomy is the removal of the primary site of RBC destruction. All therapeutic measures are described in detail in the next chapter of this book.

DAT-negative autoimmune hemolytic anemia

Approximately 3-11% of patients presenting with anemia compatible with warm-type AIHA have a negative DAT.[12] The reason for this DAT negativity may be: a) IgG sensitization below the threshold of detection by commercially available antiglobulin; b) low-affinity IgG Abs; c) RBC sensitization by IgA or, rarely, monomeric IgM Abs alone without accompanying complement fixation and thus not detectible by the commercial antiglobulin reagent that contains anti IgG and anti- C3.[2] Sensitivity tests augmented with hexadimethrine bromide (polybrene) have been developed to identify IgG Abs not detected by direct DAT.[16] Alternatively, low titers of Abs can be detected using flow cytometery.[17] Low-affinity IgG Abs are usually

Table 1. Clinical and immunological characteristics of autoimmune hemolytic anemia.

Characteristics	Warm type	Cold agglutinin disease	Paroxysmal cold hemoglobinuria	Drug-induced
Age	Variable	Middle aged, elderly	Usually child with history of URI	Variable
Clinical symptoms	Anemia, jaundice, splenomegaly	Anemia, dark urine, especially in cold weather	Acute onset of anemia, dark urine	Drug exposure, anemia, jaundice possibly dark urine
Immunoglobulin isotype	IgG	IgM	IgG	IgG
Thermal reactivity	37°C	4°C	4°C	37°C
Complement fixation	Variable	Yes	Yes	Variable
Direct anti-globulin test 37°C 4°C	IgG±C3d	 C3d C3	 C3d IgG, C3d	IgG±C3d, C3d
Plasma antibodies titter	Low/absent	High	Moderate	
Antigenic specificity	Rh and others	I/i	P	Drug-dependent antibodies*
Site of RBC destruction	Spleen	Liver, Intravascular	Intravascular	Intra- and extra-vascular
Therapy other than transfusion support	Steroids, splenectomy, rituximab	Reduce exposure to cold, rituximab	Reduce exposure to cold, self -limited	Discontinue the drug

*URI: upper respiratory infection; RBC: red blood cell. *Usually performed by expert laboratories.*

removed from the surface of RBCs during standard preparative washing of the cells at 37°C. Cold washing with low-isotonic-strength saline at 0-4°C can prevent the loss of IgG from the RBC surface, thereby retaining a positive reaction to commercial DAT reagents.[18] For the rare warm-type AIHA caused by IgA Ab or monomeric IgM Ab, DAT containing anti-IgA or anti-IgM reagents should be used.[19]

Cold agglutinin disease

Cold agglutinin disease (CAD) accounts for 15% of AIHA cases.[2] Cold agglutinin Abs are defined by their ability to agglutinate erythrocytes at an optimum temperature of 0-4°C. Most cold agglutinins are of the IgM class.[1] In the majority of patients, in addition to hemolysis, clinical manifestations include cold-induced circulatory symptoms such as Raynaud disease and acrocyanosis.[20]

Pathogenesis of the disease

Cold agglutinins are IgM Abs most often directed against the I/i blood group system.[21,22] Most are anti-I specific while the remaining show specificity for the i antigen.[1,23-25] Neonatal RBCs almost exclusively express the i antigen while I antigen predominates in individuals aged 18 months and older. Hence, cold agglutinins with anti-I specificity are more pathogenic in adults than those specific for i antigen. Cooling of blood during passage through acral parts of the circulation allows binding of cold agglutinins RBCs, causing agglutination. IgM-cold agglutinin bound to RBC antigen then binds complement protein C1, thereby activating the classic complement pathway.[26] C1 esterase activates C4 and C2, followed by the generation of C3 convertase and the formation of C3b. Upon returning to central parts of the body, with a temperature of 37°C, IgM-cold agglutinins detaches from the cell surface, allowing agglutinated RBCs to separate from one another while C3b remains bound. Some C3b-coated red cells are sequestered by the reticuloendothelial system, mainly in the liver. Complement activation may proceed beyond C3b formation to C5 activation and the assembly of the membrane-attack complex resulting in intravascular hemolysis (Figure 1-2).[27,28] C3b is converted to C3d on the surviving erythrocytes, which are released into the systemic circulation. Due to the surface-bound regulatory proteins CD55 and CD59, the complement activation is usually not sufficient to produce clinically significant activation of the terminal complement pathway. In the majority of patients, the monospecific DAT test is strongly positive for Cd3 and negative for IgM.

Laboratory diagnosis

The diagnosis of CAD is suspected by the presence of hemolytic anemia accompanied by positive DAT with C3d but not with IgG (Table 1). Following the initial findings, the antibody titer and thermal amplitude (the highest temperature at which the cold agglutinin will react with the antigen) should be determined. The latter is essential to prevent over-diagnosis because most agglutinins are clinically insignificant. An Ab titer higher than 1:512 is usually considered to be clinically significant.[20,24]

Primary cold agglutinin disease

Primary CAD is a disease of the elderly and the median age of patients is 76 years.[26] All patients have hemolytic anemia of varying degrees. The auto-Abs are usually monoclonal, most often with κ light chain.[1,28] Anti-I cold agglutinin in patients with primary CAD usually shows restriction to a specific variable domain component of the Ab heavy chain. Out of approximately 100 possible V(H) genes available, nearly all I Abs specifically use a single V(H) gene, (V(H)4-34), in the primary transcription of the heavy chain.[29,30] Over the last 15 years, it has become clear that in the majority of patients clonality at the B-cell level can be demonstrated.[28] Bernesten *et al*.[25] studied the natural history of 86 patients with primary CAD. In their study, bone marrow histology, available in 66 patients, demonstrated lymphoproliferative disease in 50 patients (76%); the lymphoproliferation was most frequently classified as lymphoplasmacytic lymphoma (50% of patients). Thus approximately half of the patients met the diagnostic criteria of both CAD and Waldestrom's macroglobulinemia (IgM monoclonal protein and ≥10% clonal lymphoplasmacytic cells in the bone marrow[31]). However, the risk of transformation to aggressive lymphoma in these patients was low (3.5% during a 10-year period).

Secondary cold agglutinin disease

CAD can be secondary to well defined malignant disease, infections or, rarely, to autoimmune disease.

CAD secondary to malignant disease: in contrast to primary CAD, the diagnosis of secondary CAD is reserved for those patients in whom the hemolytic disease complicates an overt, well defined malignant disease. The λ light chain may be involved as well as κ.[1]

CAD secondary to infection: most patients with *Mycoplasma* pneumonia produce cold agglutinins as part of the immune response. In most patients, however, no significant hemolysis occurs. The autoantibodies are polyclonal, usually anti-I specific and of the IgM class. DAT is always positive for C3d. Most patients are adults and AIHA usually occurs during the second or third week of their febrile illness. In general, the prognosis is good and the hemolytic complication subsides within 4-6 weeks. CAD also occurs in 25% of patients with Epstein-Barr virus (EBV) admitted to hospitals.[32] Transient CAD mediated by anti-I Abs has also been described following adenovirus, influenza A, varicella, rubella, *Legionella pneumophilica* pneumonia, listeriosis and pneumonia caused by chlamydia.[28]

Pathogenesis and therapeutic measures

As IgM antibodies bind to RBCs at low temperatures, an important therapeutic measure is the avoidance of exposure to cold. Splenectomy is ineffective as RBCs are being destroyed either in the liver or intravascularly. Suppression of Ab production by Abs directed against B lymphocytes (anti CD20, rituximab) currently constitutes the most effective therapy.[20,28] Addition of the purine nucleoside analog (fludarabine) to rituximab was found to increase the response rate.[33] As most IgM Abs are intravascular, plasmapheresis induces only a transient improvement. The administration of eculizumab, a monoclonal anti-C5 antibody which is a potent complement inhibitor, was shown to be effective in a few CAD patients.[34,35] The

therapeutic approach to CAD is detailed in the next chapter of this book.

Paroxysmal cold hemoglobinuria

Paroxysmal cold hemoglobinuria (PCH) accounts for 2-5% of all cases of AIHA,[2] with a higher incidence among children. Gottsche *et al*. studied 68 children with AIHA over a 4-year period and found PCH in 32.4% of them.[36] The disease is characterized by recurrent episodes of massive hemolysis following exposure to cold.[2] When first recognized during the latter half of the 19th century, it more commonly accompanied congenital or tertiary syphilis.[3] Currently, most patients diagnosed are children having a single post-viral episode.

Pathogenesis

This disease is mediated by Donath-Landsteiner IgG Ab. Following exposure to cold Donath-Landsteiner Abs and early-acting complement components bind to RBCs at the low temperature. Upon return of the cells to the 37°C central circulation, they are lysed by propagation of terminal complement. The Donath-Landsteiner-Ab itself dissociates from the RBCs at 37°C.

Laboratory features

In PCH, the DAT is usually positive during and briefly following an acute attack due to the coating of surviving RBCs with complement primary C3d fragment. The Ab is detected by the biphasic Donath-Landsteiner test, in which patient's fresh serum is incubated with RBCs, initially at 4°C and then warming of the mixture to 37°C, when intense hemolysis occurs. The Donath-Landsteiner Abs have specificity for the P blood group antigen while Ab specificities to the i antigen have also been described.[37]

Pathogenesis and therapy

PCH is usually a self-limited disease. As Donath-Landsteiner Abs and early-acting complement components bind to RBCs at low temperatures, avoidance of exposure to cold is usually beneficial.

Drug-induced autoimmune hemolytic anemia

Drug-induced immune hemolytic anemia (DIHA) is a rare serious adverse reaction resulting from drug administration, with an estimated incidence of approximately 1 per million persons.[38] The number of drugs considered to cause DIHA has substantially increased since the first report in the early 1950s. However, numerous reports of a suspected hemolytic drug reaction were based only on the observation that withdrawal of the drug led to resolution of the hemolysis, without performance of serological tests supporting an immune etiology. In 2007, Garatty and Arndt found sufficient data to support an association of DIHA with 125 medications, some of which were rarely used at that time (α-methyldopa and high-dose intravenous penicillin).[39] In recent years (2009-2011), the drugs most frequently associated with DIHA are cefotetan, ceftriaxone and piperacillin.[40] Only a few specialized laboratories perform the tests required to confirm diagnosis of DIHA.

Drugs are small-molecular weight chemicals (<1000 kDa), and therefore cannot cause an immune response by themselves. However, when complexed to a carrier molecule such as a protein they can become immunogenic. In some cases, Abs to a drug react with epitopes of drug metabolites better than with the parent drug, and therefore the metabolites are necessary for Ab detection.[40] Patients usually have a history of previously receiving the drug without any subsequent event. On the basis of the characteristics of the Abs, Garratty has recently classified DIHA into two major classes.[40] In the first, which is like AIHA, the Abs are true RBC auto-Abs, not Abs formed to the medication. It is thought that drugs evoking these Abs do so by directly affecting the immune system. These drug-independent Abs do not require the agent to be added to the *in vitro* test system in order to be detected. One example of this mechanism involves α-methyldopa; the drug alters a component of the Rh complex, resulting in an immunogenic epitope.[41] The Abs produced cross react with the new abnormal epitope, causing RBC destruction. Fludarabin is currently the medication that most commonly induces DIHA of this type.[42]

In the second class of DIHA, drug-dependent Abs are found and can be used in a diagnostic testing.[40] This class can be further divided into 2 sub-groups. The first subgroup includes drugs like penicillin and cefotetan that covalently bind to red cell membrane proteins. RBCs coated by the drug induce production of an anti- drug Ab (usually IgG*) in vivo*. The Ab attaches to the drug-coated red cells causing subsequent clearance by macrophages. On occasions, complement may also be involved in this process. These antibodies are detected *in vitro* by testing the patient's serum against commercially prepared drug-coated erythrocytes.

The second sub-group includes most of the drugs that cause acute severe intravascular hemolysis. These drugs are capable of binding non-specifically to RBC membrane proteins (not covalently as with penicillin). The Abs are formed to the combined membrane-drug (hapten) complex, can be IgM or IgG, and often activate complement. This may lead to acute rapid intravascular hemolysis, sometimes even resulting in renal failure; fatalities are more common in this group. The most common drug in this group is ceftriaxone. Arndt *et al*. reviewed the literature and identified 25 cases of ceftriaxone-induced hemolytic anemia;[43] 68% of the cases described were in children and 36% had a fatal outcome, with severe acute intravascular hemolysis. In adults, ceftriaxone-induced hemolytic anemia is less severe. In this class of DIHA, the DAT is usually positive to complement. Abs to these drugs can be detected by mixing the patient's serum with the drug and ABO-compatible RBCs.

The primary and often the only treatment necessary in DIHA, in addition to transfusion of RBCs if required, is to discontinue the suspected drug. Most drugs are cleared from the body quite quickly, and without the presence of drug even a strong drug-dependent Ab can cause no damage. A notable exception is cefotetan; with this drug, the hemolytic anemia often continues for longer than expected after the drug is stopped.[38]

Immune dysregulation in autoimmune hemolytic anemia

The breakdown of immunological tolerance and the

development of autoimmune disease is a complex process. A few murine AIHA models have been used to study the immune dysregulation in AIHA. Among these models are the New Zealand Black mouse, which spontaneously develops AIHA.[44] Disease can also be induced in healthy murine Marshal-Clarke and Playfir strains by repeated immunization with rat RBCs[45] or by the injection of C3HeB/Fej mice with a strain of lymphocytic choriomeningitis virus.[46] Studies of AIHA in human and murine models have suggested defects in the presentation of autoantigens by dendritic cells as well as B- and T-lymphocyte functional abnormalities. The putative immunopathology of AIHA is presented in Figure 1-3.

Lack of effective presentation of autoantigens

Antigen-presenting cells, including dendritic cells and macrophages, capture self-antigens from other cells and present them to autoreactive T cells to induce T-cell tolerance by either deletion and apoptosis or anergy.[47] In patients with AIHA, autoreactive T cells escape thymic selection and remain in the periphery. It has been shown that these cells could then be activated *in vivo* in patients with AIHA, but not in healthy controls.[48]

Functional abnormalities of B cells

Polyclonal activation of B cells by superantigens or mitogens has been suggested as a possible mechanism by which viruses trigger autoimmune disease. With intracerebral inoculation of the lymphocytic choriomeningitis virus, the CH3cB/FeJ mouse develops AIHA and hypergammaglobulinemia.[49] In humans, several virus and parasite infections are followed by an increased production of auto-antibodies and AIHA.[2] In chronic graft-*versus*-host disease, activation of host B cells by donor T cells induces autoimmunity, including warm-type AIHA.[50]

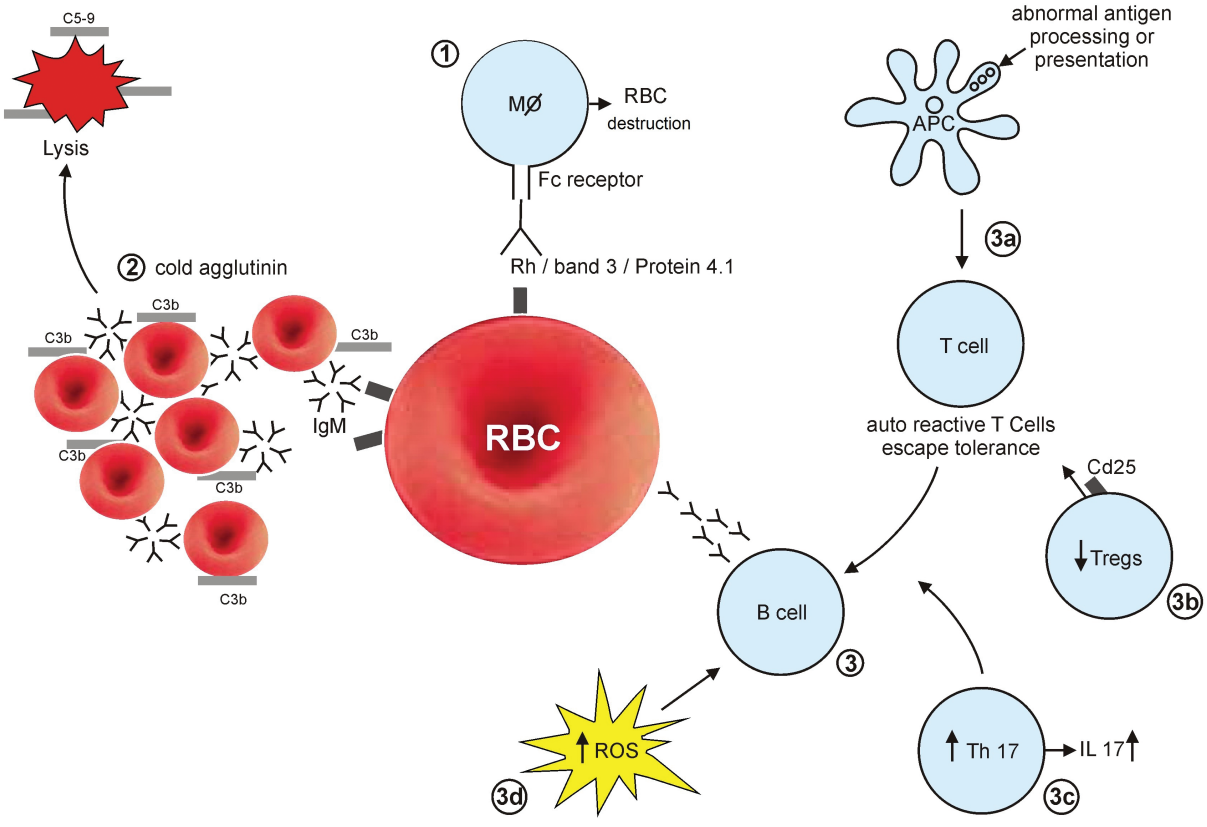

Figure 1. Immunopathogenesis of autoimmune hemolytic anemia. (1) IgG Abs against Rh, band 3, protein 4.1 or other RBC antigens are generated. The antibody-coated RBCs bind to the Fc-receptor on macrophages mainly in the spleen, resulting in RBC membrane damage or destruction. (2) In CAD, anti I/i IgM Abs are produced. The IgM pentamer causes RBC agglutination and complement activation, resulting in RBC lysis. (3) Autoantibodies are generated by B lymphocytes following different stimuli such as polyclonal activation of B cells by superantigens. (3a) Abnormal processing of antigens by dendritic cells causes an immune stimulus to a self-antigen instead of signaling toward apoptosis and deletion. (3b) Reduced number of Tregs allows auto-reactive T cells to escape tolerance. (3c) Elevated number of Th17 cells and increased serum IL17in AIHA correlate with degree of anemia. (3d) Elevated reactive oxygen species (ROS) augments production of auto-Abs to RBCs. M: macrophage; APC: antigen presenting cells; RBC: red blood cell; ROS: reactive oxygen species.

Functional abnormalities of T cells

Although AIHA is caused by anti-RBC Abs produced by B lymphocytes, the generation of auto-antibodies is a T-cell dependent process. This was shown in New Zealand Black mice, in which treatment with anti-CD4 monoclonal antibody retarded IgG autoantibody production.[51] Depletion of T cells from such mice prevented the induction of AIHA in response to immunization by rat RBCs.

The current dogma suggests that autoimmune diseases are characterized by imbalance between pro-inflammatory and anti-inflammatory mechanisms.[52] The recently recognized Interleukin 17 is produced by pro-inflammatory Th17 cells.[53] On the other hand, regulatory T cells (Tregs) marked by $CD4^+CD25hi\ Fox3^+$ have an important role in maintaining self-tolerance.[54] It has been suggested that Tregs counter Th17 cells and reduce their autoimmune potential.[52] Both a decrease in Treg cells and an increase in Th17 cells have been documented in AIHA.

The role of Tregs in the development of AIHA was demonstrated by using the Marshal-Clarke and Plyfair model of murine AIHA in which mice repeatedly immunized with rat RBCs develop erythrocyte autoantibodies. Treatment of these mice with anti CD25 Abs prior to immunization with rat RBCs increased the incidence of AIHA from 30% to 60%.[55] Adoptive transfer of purified Tregs but not $CD4^+CD25^-$cells from immunized mice into naive recipients prevented the induction of the AIHA. Regulatory T cells specific for RBC auto-antigens have been recovered from patients with AIHA.[56] Significantly lower numbers of Tregs were found in a small group of patients with AIHA compared to healthy controls.[57] These findings may suggest a critical role for Tregs in the development of AIHA. Patients with AIHA have also been found to have an elevated number of Th17 cells which closely correlated with the disease activity.[58] Two recent studies measuring serum IL-17 in AIHA patients also suggested that IL-17 levels correlated with the degree of anemia.[59] Furthermore, using the Marshal-Clarke and Playfir model of murine AIHA, adoptive transfer of Th17 cells heightened the initial anti-rat RBC Ab response and increased the onset of AIHA. *In vivo* neutralization of IL-17 abrogated the development of AIHA.[58]

Oxidative stress

Oxidative stress with overproduction of reactive oxygen species (ROS), known to be highly immunogenic, can induce Ab production in autoimmune disease.[60] Augmented production of auto Abs to RBCs was found in superoxide dismutase 1 (SOD1)-knockout mice.[61] Anemia induced by the absence of SOD1 was caused by accelerated hemolysis in blood plasma and phagocytic removal of RBCs by liver macrophages.[62] The $SOD1^{-/-}$ mice were rescued by local expression of human SOD1 in RBCs. Elevated oxidative stress in RBCs was also observed in New Zealand Black mice. Transgenic overexpression of human SOD1 in erythroid cells led to prolonged survival in these mice.[63,64]

Conclusions

Although the basic mechanisms of red blood cell destruction in AIHA have been clarified over the years, the loss of immune tolerance to RBC antigens is a complex process and is still poorly understood. Recently, T-cell dysregulation with a decrease of Tregs and an increase of Th17 cells has been documented in AIHA and probably plays a role in the pathogenesis of the disease. Increased oxidative stress has also been suggested to induce auto-antibody production. Further understanding of the pathogenesis will eventually enable more effective therapy to be developed.

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