Erythrocyte Auto-Antibodies against Complement Regulatory Proteins of the Erythrocyte Membrane

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Abstract

Introduction: Normally erythrocytes are protected from complement-mediated lysis by the action of regulatory proteins present in their membrane: complement receptor 1 or CR1-CD35; degradation accelerating factor, DAF or CD55 and CD59. Although the contribution of these molecules has been well understood in paroxysmal nocturnal hemoglobinuria and systemic lupus erythematosus, their role has been little explored in autoimmune hemolytic anemia caused by warm antibodies.

Objective: To detect the presence of autoantibodies against CD35, CD55 and CD59 in patients with autoimmune hemolytic anemias due to warm antibodies and their relationship with the intensity of hemolysis.

Method: 141 blood samples from patients with active warm autoimmune hemolytic anemias were studied in the immunohematology laboratory of the Institute of Hematology and Immunology; La Habana, Cuba, in the period among 2000 - 2016 and the specificity of erythrocyte auto-antibodies was determined using of immobilization of erythrocyte antigens with monoclonal antibodies assay.

Results: Auto-antibodies against CD35, CD55 and CD59 were detected in 37.7% of the samples analyzed, which was significant (p = 0.00) with the intensity of the hemolytic phenomenon.

Conclusion: Patients with autoimmune hemolytic anemia due to warm antibodies may present auto-antibodies against the complement regulatory proteins present in erythrocytes; these antibodies are related to the severity of the hemolytic anemia.

Keywords: CD35; CD55; CD59; Erythrocyte Auto-Antibodies; Warm Autoimmune Hemolytic Anemia; Complement System; Complement Regulatory Proteins

Abbreviations

AIHA: Autoimmune Hemolytic Anemia; Ab: Antibody/Antibodies; Auto-Ab: Auto-Antibody/Auto-Antibodies; Ag: Antigen/Antigens; Auto-Ag: Auto-Antigen/Auto-Antigens; wAIHA: Warm Autoimmune Hemolytic Anemia; CR1-CD35: Complement Receptor 1; DAF-CD55: Degradation Accelerating Factor; PNH: Paroxysmal Nocturnal Hemoglobinuria; SLE: Systemic Lupus Erythematosus; DAT: Direct Antiglobulin

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Test; RBCs: Red Blood Cells; EDTA: Ethylenediaminetetraacetic Acid; PBS: Phosphate Buffered Saline; BSA: Bovine Serum Albumin; MoAb: Monoclonal Antibody; PMSF: Phenylmethylsulphonylfluoride; OPD: o-Phenylenediamine; Allo-Ab: Allo-Antibodies; MAC: Membrane Attack Complex; TLR: Toll Like Receptor; APC: Antigen Presenting Cells

Introduction

Autoimmune hemolytic anemia (AIHA) is caused by destruction of erythrocytes mediated by autoantibodies (auto-Ab) that recognize antigens (Ag) of erythrocyte blood groups. To explain the loss of immunological tolerance towards auto-antigens (auto-Ag), as well as the mechanisms involved in increasing the destruction of these cells, different studies have been designed, in animal models and in humans [1].

The activation of the complement system by the classical pathway is one of the mechanisms of immune destruction of erythrocytes in the context of AIHA anemia due to warm antibodies (wAIHA), product of the incomplete activation of this system up to C3 and the subsequent erythrophagocytosis pathway, via C3 receptor present in macrophages.

Normally erythrocytes are protected from complement-mediated lysis by the action of regulatory proteins present in their membrane: complement receptor 1 (CR1-CD35); degradation accelerating factor (DAF-CD55) and CD59. Although the contribution of these molecules has been well understood in paroxysmal nocturnal hemoglobinuria (PNH) and in systemic lupus erythematosus (SLE) [2], their role has been little explored in wAIHA.

There are no reports in the reviewed literature that document the detection of erythrocyte auto-Ab directed against the Ag of the Knops and Cromer blood groups located in the CD35 and CD55 proteins, or on CD59, nor has their presence been related to the intensity of the hemolysis in patients with wAIHA, so it is interesting to detect the presence of auto-Ab against CD35, CD55 and CD59 in patients with wAIHA and its relationship with the intensity of hemolysis.

Materials and Methods

Population study

141 blood samples from patients with active wAIHA were studied in the immunohematology laboratory of the Institute of Hematology and Immunology, in the period among 2000 and 2016; of them 89 (63.1%) corresponded to the female sex and 52 (36.9%) to the male sex. In 58.1%, wAIHA was presented idiopathically and in 41.8%, secondary to other diseases. 22.6% were presented as negative direct antiglobulin test (DAT) that was diagnosed by the presence of auto-Ab in the eluate of erythrocytes and through an immunoenzymatic assay for the quantification of auto-Ab associated with red blood cells [3]. The age range of the patients was 1 - 84 years (Median: 45 years).

Blood samples and ether elution

After informed consent had been obtained from patients and blood donors, blood samples were collected from venous blood in EDTA (VACUETTE®). The samples were centrifuged at 270g for 8 minutes at room temperature, and the plasma and buffy coat were removed.

Ether eluates were prepared after washing 1 mL of packed RBCs x 10 using 10 volumes of saline. Elution was performed by adding 1 mL of PBS, pH 7.2, containing 0.4% BSA (Sigma-Aldrich Co.) and 1 mL of diethyl ether (Sigma-Aldrich Co.) to 1 mL of RBCs (an average of 1.1 x 10¹⁰ RBCs). The mixture was incubated in a 37°C water bath for 10 minutes, with frequent mixing. After centrifugation, the upper layer of ether was discarded and the hemoglobin-stained eluate was transferred into a test tube. The residual ether was evaporated at 37°C for 15 minutes. An average of 1 mL of eluate was recovered. Eluates were kept frozen at -80°C until used.

**MAIEA assay**

The specificity and isotype of auto-Ab was performed by MAIEA assay described by Petty AC., *et al.* 1993 [4].

**Principles and methodology of MAIEA**

The basis for a positive MAIEA reaction is that two Ab, one a human Ab, the other mouse monoclonal antibody (MoAb), are specific for the same protein, but have epitopes on different regions of the protein. The two Ab are incubated with a red cell suspension at 37°C for at least 1h, thus the Ab are permitted to react with the native protein before the epitopes are potentially denatured during membrane solubilization. The two Ab and the targeted protein form a trimolecular-complex that is released from the membrane by lysis and solubilization. The trimolecular-complex is captured by the goat anti-mouse IgG via the MoAb and is detected by addition of peroxidase conjugated goat antihuman globulin, which binds to the trimolecular complex via the human Ab. The colored product is measured by the absorbance reading at 492 nm in an ELISA reader. Usually, a ratio greater than 2:1 is considered positive [5]. In our case the human Ab used is the auto-Ab which is present in eluate obtained from the patient with wAIHA.

**Precoating of microtitre plates**

Microtitre plates (Nunc, Immunoplates) were precoated with 100 μL per well of 1/500 IgG-Fc specific goat anti-mouse (Serotec) in 0.05M carbonate buffer at pH 9.6. The plate was left overnight at 4°C and the following morning washed four times with 250°C PBS/Tween 20 0.05%/Triton X-100 0.5% (PBS-TTw) (Sigma-Aldrich Co.), pH 7.4. The final wash was left for 30 minutes at 4°C to block excess binding sites.

**Preparation of red lysate membrane component-antibody complex**

It was prepared a 10% red cell suspension from 10 blood donor’s pool of O blood group negative DAT washed three times. 80 μL of this suspension was incubated with 40 μL of mouse MoAb with known specificity toward a membrane component and 40 μL of eluate containing human auto-Ab, for 60 minutes at 37°C. The sensitized red cells were then washed three times with isotonic saline solution and cell lysis was obtained by the addition of 200 μL of 0.01M Tris-HCl; 0.15M NaCl; 2.5% Triton X-100; containing 2 mM of protease inhibitor PMSF (phenylmethylsulphonylfluoride, Sigma-Aldrich Co.). The subsequent lysate was maintained at 4°C for 30 minutes to permit complete solubilization of the red cell membrane and then centrifuged at 150g for 15 minutes to remove the cytoskeleton. 120 μL of each supernatant were diluted with 400 μL of PBS-TTw.

**Detection of monoclonal antibody-specific immobilization of erythrocyte antigens**

Of the diluted red cell lysates, 100 μL were added to the precoated microtitre wells and incubated overnight at 4°C. The plate was then washed four times with PBS-TTw before adding 100 μL per well of IgG and IgM Fc-specific peroxidase-conjugated goat anti-human (Serotec), diluted 1/5000; and IgA Fc-specific peroxidase-conjugated goat anti-human (Serotec) diluted 1/2000. The plate was incubated with the peroxidase conjugated antibody for 1h at 37°C and then washed five times with PBS-TTw.

A substrate solution (100 μL per well) of 0.24 mg/mL of OPD (o-phenylenediamine, Sigma-Aldrich Co.) in 0.05M phosphate citrate buffer, pH 5.0, with 0.024% of hydrogen peroxide (Sigma-Aldrich Co.) was added. The colour reaction was stopped after 15 minutes by adding 100 μL of 4N sulphoric acid (Sigma-Aldrich Co.) and the absorbance was read on an ELISA reader (ChemWell 2910) at 492 nm.

**Expression of results**

The results were expressed as change in absorbance; the difference between the eluate test with those with antibody-negative eluate. Ratios of greater than 2.5:1 of absorbance values were considered in our study.

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Determining the specificity and isotype of erythrocyte auto-Ab

The specificity and isotype of auto-Ab was performed by MAIEA assay, described before [4]; with the use of murine MoAb that recognize the Ag of blood group systems: anti-CD35 [Knops (KN), clone E11, Serotec, UK], anti-CD55 [Cromer (CROM), clone BRIC 216, Serotec, UK] and anti-CD59 [clone MCA 1927, Serotec, UK] and peroxidase-labeled anti-IgG (Serotec, UK), anti-IgA (Serotec, UK) and anti-IgM (Serotec, UK) Ab.

The specificity and isotype of auto-Ab were related to the degree of hemolysis and the presence of more than one isotype of immunoglobulins. The intensity of hemolysis was classified according to the concentration of hemoglobin (Hb); the reticulocyte count and the plasma haptoglobin figures. In the group with high-grade hemolysis (H1), those cases that presented Hb levels less than 90 g/L, reticulocyte count greater than 5% and haptoglobin values less than 0.4 g/L were considered and in the group with low-grade hemolysis (H2) in those cases that presented Hb levels between 90 and 105 g/L, reticulocyte count between 3 and 5% and normal plasma haptoglobin values.

The isotype and immunoglobulins’s combinations were expressed in absolute and relative frequencies. The Chi-square test ($\chi^2$) was used in all comparisons and a value of $p <0.05$ was considered significant.

The ethical principles related to medical research were respected [5].

Results and Discussion

Auto-Ab against complement regulatory proteins were detected in 37.7% of the samples (n = 56); of them 4.2% (n = 6), 20.5% (n = 29) and 27.6% (n = 39), corresponded to CD35, CD55 and CD59 respectively. In all the cases in which auto-Ab was detected against CD35, Ab of the IgA and IgM isotypes were identified without the presence of IgG; in contrast to the auto-Ab anti-CD55 and anti-CD59 in which the IgG and IgA isotypes predominated, respectively (Table 1).

<table>
<thead>
<tr>
<th>Auto-Ac</th>
<th>Immunoglobulin isotypes and combinations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgG</td>
</tr>
<tr>
<td>Anti-CD35</td>
<td>0</td>
</tr>
<tr>
<td>Anti-CD55</td>
<td>22 (75.8)</td>
</tr>
<tr>
<td>Anti-CD59</td>
<td>5 (12.8)</td>
</tr>
</tbody>
</table>

*Table 1: Relationship between the presence of anti-CD35, CD55 and CD59 autoantibodies and immunoglobulin isotypes.*

To date, very few studies have been published regarding the specificity of auto-Ab in AIHA. Previous research shows specificities in less than 50% of cases, with agglutination techniques and with the use of high incidence Ag-deficient erythrocytes [6]. The results of this study reveal that specific auto-Ab can be detected in patients with AIHA against complement regulatory proteins present in erythrocytes such as CD35, CD55 and CD59. Previously, the MAIEA assay had not been used for these purposes, which limits the comparison of the findings, although this constitutes the first report.

The Ag of the Knops blood group system are located on complement receptor 1 (CR1 or CD35) which is a member of the complement regulatory protein superfamily. This 200 kDa glycoprotein is present in erythrocytes, granulocytes, monocytes, B lymphocytes, T cell subtypes, glomerular podocytes, and in follicular dendritic cells. Its function prevents excessive complement activation by inhibiting the C3 and C5 convertase of the three complement pathways, regulating the deposition of C3 fragments on the erythrocyte membrane, and serving as a cofactor for factor I for the degradation of C3b [7].

Ab against CD35 are classified as “high titer and low avidity” Ab, they are generally considered problematic to work with due to variations in the expression strength of Ag and because it is difficult to absorb the antibody or obtain active eluates from weakly positive cells and consequently, it is almost impossible to distinguish negative cells. They are generally of the IgG class, although they are also reported of the IgA class [2]. In the study, Ab directed against CD35 were detected in 6 samples, but unlike previous reports, they corresponded to the IgA and IgM isotypes. One of the possible explanations for the non-detection of Ab of the IgG isotype against CD35 may be a greater avidity of the Ab IgA and IgM for Ag and a higher concentration of these that would occupy a greater number of antigenic sites and therefore would not allow IgG Ab bind to Ag. On the other hand, Ab of the IgM isotype was detected and this data is not collected in the reviewed literature, this could be explained by the greater sensitivity of the immunoenzymatic assay used.

The degradation accelerating factor (CD55) is a protein anchored to glucosylphosphatidylinositol in the erythrocyte membrane that inhibits the cleavage of C3 and C5, thus accelerating the degradation of C3 and C5 convertase. In this molecule the Ag of the Cromer system are located. The Ab directed against these Ag are generally of the IgG class [2], as found in the research. However, in the study carried out, Ab of the IgA and IgM isotypes were also detected. Probably due to the use of the MAIEA assay for the detection of the specificity and the isotype of the Ab involved, this allows eliminating the interference produced by other molecules.

The CD59 molecule is a glucosylphosphatidylinositol-anchored protein that inhibits the formation of the membrane attack complex (MAC) by binding to C8 and C9. Few studies have been conducted on CD59 in the context of autoimmunity and specifically in AHAICs. In 2014, CD59 was accepted as a blood group system due to documented evidence of allo-antibodies (allo-Ab) detected in children deficient in this molecule who received blood transfusions. The reports indicate that these Ab are of the IgG class, detected by gel inhibition and agglutination techniques [8,9]. Our results show the presence of auto-Ab of the IgG, IgA and IgM isotypes with a predominance of IgA.

A possible explanation for the predominance of auto-Ab of the IgA isotype could be that the sugars present in the molecule were immunodominant and induced an isotype switch to IgA after the primary response in the context of a T-independent type II response. On the other hand, recent studies suggest that they are normally distinguished as Ag carbohydrates with highly organized repetitive structures that extensively cross-link B cell receptors, directly delivering strong activation signals to B cells and a rapid induction of low affinity antibodies, predominantly IgM. Although exposure to T-cell-independent type II Ag can result in the production of IgG and IgA, the mechanism by which class switching occurs in response to a T-cell-independent type II antigen is not yet available well clarified [10].

Previous studies show that CR1/2 ligation of C3 together with the cross-linking of the B cell receptor and CD4+ T cell-derived cytokines may be important in the production of Ab after exposure to Ag. However, unlike this classical paradigm, in which Ag are believed to be intrinsically dependent or independent of T cells, the ability of CD59 to induce a humoral response dependent on CD4+ T cells only in the absence of C3 or CR1/2 demonstrates that, in addition to biochemical characteristics of a given immunogen, extrinsic immune factors, such as complement, may possess the unique ability to regulate whether Ag itself induces an Ab response through a T-cell-dependent or independent pathway [10].

One of the best established pathogenic mechanisms for auto-Ab is the cytotoxic destruction of cells, subsequent to the recognition of Ag on the cell surface. Cell destruction can occur in different ways, the most common being by activation of the complement system.

The implication of the complement system in the pathogenesis of AIHA is still controversial. Experimental studies in mice demonstrate that erythrocytes from CR1-deficient mice are spontaneously cleared in vivo by the complement system. Those deficient in CR1/DAF are spontaneously eliminated by the alternative pathway when they are opsonized with auto-Ab IgG2a anti-CR1. On the other hand, DAF-deficient erythrocytes are cleared more rapidly by complement than by the Fc receptor pathway. These findings suggested that CR1 (CD35) and DAF (CD55) influence the hemolytic pathway in wAIHA. CD55 and CD59 have been extensively studied in the context of PNH and SLE, and their deficiency has been found to lead to complement-mediated hemolysis. Similarly, it has been reported that patients with primary or secondary AIHA may have a deficiency in the expression of CD59 in their erythrocytes [11,12].

In this study, the presence of auto-Ab anti-CD35, CD55 and CD59 was evaluated in the erythrocytes of patients with active AIHA. The presence of erythrocyte auto-Ab against complement regulatory proteins present in erythrocytes would imply a blockage or neutralization of these and therefore could be more sensitive to the action of complement.

Acquired deficiencies of complement regulatory proteins in erythrocytes occur in various autoimmune diseases where the level of expression, determined by cytometric assays, is decreased. CD3+ lymphocytes with decreased expression of CD55 and CD59 are also observed in patients with SLE compared to lymphocytes from healthy individuals, as in patients with autoimmune thrombocytopenia [11]. A possible explanation would be that the decrease in the expression of these molecules may be the result of the blocking of these by the auto-Ab which prevents their determination by these techniques. This constitutes the first study in which auto-Ab against CD35, CD55 and CD59 have been detected by MAIEA assay.

A recent study has suggested the relationship between complement/TLR and its interaction with differentiation into Th17 cells, which constitutes new evidence on the mechanism of action of complement and autoimmunity. This study has shown that the coincident activation of complement and various TLRs in mice leads to the synergistic production of serum factors that promote Th17 differentiation from the use of anti-CD3/CD28 or antigenic stimulation of T cells [13]. These results are reinforced by other studies that suggest that IL-17 production is more strongly associated with AIHA than with IFN-γ production. The most relevant finding suggests that IL-17A was the most prominent cytokine in the response of patient T cells to autologous erythrocytes as a source of Ag. This result raises the possibility that autoreactive Th17 cells contribute to the pathogenic activity of Th cells in AIHA and is responsible for at least some effects attributed to the Th1 subtype [14,15].

The presence of auto-Ac against these 3 complement regulatory molecules was significant (p = 0.00) with the intensity of the hemolytic phenomenon (Table 2). In all patients, the presence of such auto-Ac was related to high-grade hemolysis, which suggests that these findings could be of clinical importance. However, the literature shows that CD35 is of less importance than CD55 and CD59 in the protection of erythrocytes from complement-mediated lysis, so it would have to be analyzed whether in patients in which only auto-Ab was detected against CD35 other specificities of blood groups could be present that could exacerbate hemolysis in patients with wAIHA.

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Degree of Hemolysis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD35</td>
<td>H1: 2</td>
<td>H2: 0</td>
</tr>
<tr>
<td>Anti-CD55</td>
<td>H1: 9</td>
<td>H2: 5</td>
</tr>
<tr>
<td>Anti-CD59</td>
<td>H1: 18</td>
<td>H2: 4</td>
</tr>
<tr>
<td>Anti-CD35+55</td>
<td>H1: 1</td>
<td>H2: 0</td>
</tr>
<tr>
<td>Anti-CD35+59</td>
<td>H1: 3</td>
<td>H2: 0</td>
</tr>
<tr>
<td>Anti-CD55+59</td>
<td>H1: 10</td>
<td>H2: 4</td>
</tr>
<tr>
<td>Total</td>
<td>H1: 43</td>
<td>H2: 13</td>
</tr>
</tbody>
</table>

*Table 2: Relationship between the presence of anti-CD35, CD55 and CD59 autoantibodies and the intensity of the hemolytic phenomenon.*

H1: High-Grade Hemolysis; H2: Low-Grade Hemolysis; p = 0.00.

On the other hand, the authors suggest that in wAIHA the destruction of erythrocytes is predominantly extravascular due to the modest activation of the complement system combined with the physiological protective effect of the CD55 and CD59 molecules of the erythrocyte membrane [16]. However, the results of the present study reveal that the presence of auto-Ab against CD55 and CD59 has significance with the hemolytic phenomenon and this is more prominent whenever the CD59 molecule is blocked by auto-Ab, so it should

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be analyzed the hemolytic process in wAIHA as a multifactorial phenomenon that depends on factors such as the class of immunoglobulin, the number of immunoglobulins that act and their molecules that are opsonizing the erythrocytes; of the affinity of the Ab produced by their specific Ag, of the complement system, of the specific receptors for the Fc fraction and complement fragments present in the mononuclear phagocytic system and in NK cells, that the anemia is idiopathic or secondary to a specific disease and the biological function of the erythrocyte Ag involved, such as CD55 and CD59. According to the predominance of factors, the system would move towards a predominantly extravascular destruction with a lower rate of intravascular or predominantly intravascular destruction, without ruling out extravascular hemolysis or, if it occurs to a lesser extent.

At the same time, the detection of auto-Ab with combined specificities such as anti-CD35+55, anti-CD35+59 and anti-CD55+59 in the same sample of patients with wAIHA is interesting. This finding can be explained by the epitope spreading, a phenomenon studied and reported by Hall AM., et al. 2007.

This author, in experimental studies of NZB mice genetically engineered proved the lack of the dominant RBC autoantigen Band 3 which has allowed dissection of the underlying mechanisms of spontaneous AIHA. The main results of NZB AIHA’s induction are not dependent on expression of the major auto-Ag. In its absence, antibodies are not detected against Band 3, and the corresponding helper response is greatly attenuated, but, instead, high levels of auto-Ab with other RBC specificities are generated. The immune defect is therefore specific for the RBC type, rather than for the dominant auto-Ag. The shift in the specificity of the auto-Ab response in these models indicates that the potential for auto-aggression is not limited to Band 3 and is consistent with the point of view that a variety of Ag from the target cell may be processed and/or presented in a more immunogenic fashion to drive autoimmune disease. For example, aberrant handling of RBCs by APC would be a predisposition to autoimmune responses against a range of potential auto-Ag. Such a change may arise from activation of APC, or recruitment of nonprofessional APC types, in response to innate immune signals. Once autoimmunity is initiated, propagation of the response may occur through epitope spreading, ultimately leading to auto-immunization against multiple self-epitopes [17].

Conclusion

The MAIEA assay is a sensitive method that can be used for specificities and isotypes determinations of auto-Ab in patients with wAIHA. Patients can present auto-Ab directed against the complement regulatory proteins CD35, CD55 and CD59 present in erythrocytes. These auto-Abs are related to the severity of anemia and that the decreased expression of these molecules in different autoimmune diseases may be the result of their blockage by auto-Ab, which contributes to their complement-mediated destruction. This study once again corroborates the complexity of mechanisms and factors, and their clinical significance in AIHA.

Conflict of Interest

The authors declare that there are no conflicts of interest of any kind.

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