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Red blood cell allo- and autoimmunization and microbes: Two sides of the same coin

Carlos A Gonzalez, Silvana Gonzalez

Developing antibodies against antigens on red blood cells (RBCs) is an important public health and health care problem. In fact, the clinical consequences include difficulty in finding compatible RBC units therefore causing a delay in transfusion and treatment, hemolytic disease of the newborn and hemolytic transfusion reaction, which can be fatal in some cases.

The explanation of why only a selected group of patients (respondents) develop RBC alloantibodies (due to transfusion or pregnancy) is complex and poorly understood.

A recent epidemiological study on risk factors of RBC alloimmunization shows that alloimmunization is more frequent in women than in men, in RhD negative than in RhD positive, and the primary diagnosis is associated with a greater or lower probability to be respondent [1]. The diagnosis of sickle cell disease, systemic lupus erythematosus, rheumatoid arthritis, and myelodysplastic syndrome was more common among respondents than among the non-responders.

This situation is not unexpected, as previous studies indicated the existence of a greater risk of alloimmunization when the transfusion receiver is in a proinflammatory state, such as autoimmune, infectious and oncohematological diseases [2]. This state of immune activation, caused by genetics and epigenetics, strengthens The response and is essential for the development of the humoral immunity to RBC alloantigens.

The host–microbe is of interaction immunohematological consequences. Some can be considered physiological (since they contribute to the immune repertoire), some are temporary, and others are clinically significant, and may be fatal.

The first host–microbe interaction occurs during the first weeks of extrauterine life which generates a T-cell-independent immune response to carbohydrates and glycolipids present in bacterial membrane and the ABO antibodies are produced. In the next few months/years and as an integral part of the T-cell-independent immune response to bacteria, the "natural" blood group antibodies are generated (H, Le, and MNS) mostly IgM, low affinity IgG2/IgG4, and if they do not trigger complement, they tend to be clinically not significant [3].

A second kind of microbe–RBC interaction causes alterations in blood group antigens, whether by their potentiation (T, Tk, Th, and Tn); by their depression, such as Knops in Acquired Immunodeficiency Deficiency Syndrome (AIDS) or A, B, H, I, K, M, and N in sepsis; or by acquiring them (B_{acq}, K_{acq}, Jk^{b}_{acq}). These phenomena are usually transient and remit spontaneously or due to medical treatment.

The third host–microbe interaction, not always clinically distinguishable from the previous ones, is produced by pathogenic carriers of sequences of peptides that are similar to blood group antigens, capable of generating a primary immune response (T-cell-dependent). This could explain the relationship between infection and the detection of alloimmune antibodies. Animal models strongly support this observation; as a matter of fact, viral infections or viral-like inflammation can potentiate alloimmunization [4].

Another phenomenon can be observed due to host–microbe interaction, which is the possibility of generating autoimmune responses in the context of certain infections. There is a strong relationship between infections and the development of anti-RBC autoantibodies. Several mechanisms, not mutually exclusive, have been proposed: (a) Molecular mimicry (an immune response to a microbial antigen which generates cross-reactive antibodies that recognize and destroy host antigens), (b) Escape from thymic deletion by autoreactive clones, and (c) T-B dysfunction which causes a decrease in Tregs cells, an increase in Th2; it may even generate a polyclonal B cell activation.

A situation that deserves our attention is Human Immunodeficiency Virus (HIV)-infected individuals, which by direct effect of the virus or by its associated infections are characterized by:

Carlos A. Gonzalez[1], Silvana Gonzalez[2]

Affiliations: [1]Servicio de Hemoterapia, Hospital Muñiz, Buenos Aires, Argentina; Dirección de Posgrado, Medical School, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina; [2]Medical School, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina.

Corresponding Author: Dr. Carlos A. Gonzalez, Servicio de Hemoterapia, Hospital Muñiz, Buenos Aires, Argentina, Uspallata 2272, Buenos Aires, Argentina; Email: carlosgonzalez@buenosaires.gob.ar

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Lower prevalence of anti-RBC alloantibodies: One of the first consequences of the action of HIV is the decrease of alloimmune response upon exposure to allogeneic RBC [5] due to the qualitative and quantitative CD4 T cell declines, a vital subpopulation in the recognition, processing, and presentation of blood group antigens by antigen-presenting cells. Consequently, the incidence of irregular antibodies in HIV infected is 0–2% [2].

Higher prevalence of anti-RBC antibodies: 10% of HIV-infected patients present anti-RBC autoantibodies, reaching a prevalence of 85% in AIDS [6]. Autoimmune hemolytic anemia occurs in 3% of them, its risk 28 times higher than control group [7]. Even in those patients treated with antiretroviral therapy, the prevalence can be the same or even higher [8]. When studied properly, immune hemolysis can be drug induced [9].

In conclusion, infected patients constitute a heterogeneous group with different underlying conditions, microorganisms of diverse virulence, and a wide range of inflammatory capacity and response as a host; therefore, the immunohematological consequences of direct and indirect action of microbes in the host from not clinically significant to life-risking; the specialist must be alert in order to enable their early detection and differential diagnosis [10].

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Keywords: Alloantibodies, Autoantibodies, Blood group antibodies, Immune response

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Author Contributions

Carlos A Gonzalez – Conception of the work, Design of the work, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Silvana Gonzalez – Conception of the work, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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