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Review

Red blood cell alloimmunization immunogenetic risk factor

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Alloimmunization to blood group antigens is the result of a humoral immune response initiated by exposure to foreign antigens absent from the recipient's red blood cells (RBCs). Interestingly, not all individuals who receive mismatched RBC transfusions develop alloantibodies. Increasing evidence points to the role of the classical human leukocyte antigen (HLA) system in modulating this immune response. More recently, polymorphisms in nonclassical HLA molecules have been implicated in the regulation of inflammatory responses, particularly in patients with sickle cell disease. The role of natural fetomaternal microchimerism may also be a factor to consider in explaining individual variability in alloimmune response.

The genetic diversity of both RBC antigens and HLA across ethnic groups underscores the need for high-throughput sequencing technologies to improve donor–recipient matching. In the future, genotyping strategies should aim not only to assess individual risk for alloantibody development but also to guide the selection of compatible RBC units, thereby reducing the likelihood of alloimmunization.

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Alloimmunization against blood group antigens is a humoral immune response triggered by exposure to antigens absent in the recipient but present on transfused red blood cells. This response is based on adaptive immunity, which is highly specific and able to generate immune memory. Following re-exposure to the same antigen, the immune system produces a faster and stronger response.

The adaptive immunity and human leukocyte antigen system

Adaptive immunity requires the cooperation of antigen-presenting cells (APCs), B lymphocytes, and T lymphocytes. T cell receptors recognize antigens when they are bound to membrane proteins called major histocompatibility complex molecules or human leukocyte antigen (HLA) system in human. Classical HLA class I (HLA-A, -B, -C) and nonclassical HLA (HLA-G, -E, -F) are expressed by all cells, with varying density. Class II molecules (HLA-DR, -DQ, -DP) are expressed by APC cells. HLA molecules contain variable regions that form peptide-binding pockets (P1–P9). Certain residues — especially at positions 13, 70, 71, 74 et 78 of the DRB1 gene — play a crucial role in determining T cell recognition and immune outcomes. These polymorphisms influence both alloimmunization and susceptibility to autoimmune diseases.

T lymphocytes are divided into two main subsets: CD8+ cytotoxic T cells, which recognize peptides presented by class I HLA molecules, and CD4+ helper T cells, which respond to class II restricted peptides. CD4+ T cells are essential for activating B cells and promoting antibody production, making them central players in alloantibody formation. Therefore, variations in HLA class II genes — particularly DRB1— can significantly impact an individual's ability to mount an immune response to foreign antigens.

HLA analysis has been revolutionized by advances in molecular typing. Since 2013, next-generation sequencing (NGS) has overcome many of the limitations of previous techniques by enabling high-resolution, high-throughput allele typing. In spite of its technical requirements, NGS allows for the complete sequencing of HLA genes and the rapid analysis of large volumes of samples. Underscoring the complexity and importance of personalized HLA typing in transfusion and transplantation medicine, more than 41 000 HLA alleles have been identified to date, including more than 3800 DRB1 variants [1].

Blood group

To date, the International Society of Blood Transfusion (ISBT) has approved 47 human red blood cell (RBC)

Nomenclature

APCs	antigen-presenting cells.
CD	cluster of differentiation.
FY	Duffy.
GvHD	graft-versus-host disease.
HLA	human leukocyte antigen.
HPA	human platelet antigen.
HNA	human neutrophil antigen.
JK	Kidd.
KEL	Kell.
MHC	major histocompatibility complex.
NGS	next-generation sequencing.
NIMA	maternal non-inherited antigens.
RBC	red blood cells.
RH	Rhesus.
SCD	sickle cell disease.

blood group systems, including 362 antigens [2]. These antigens are classified according to strict ISBT criteria: They must be defined by a human alloantibody, have a hereditary pattern, be encoded by a sequenced gene at a known chromosomal location, and be genetically distinct from previously identified systems. Blood group antigens can be proteins or carbohydrates, most commonly resulting from single-nucleotide polymorphisms (SNPs). These SNPs can allow antigen expression, create new antigens, or result in weakened or absent expression. More complex mechanisms may also influence blood group phenotypes.

In the population, the frequency of antigens varies considerably: 184 antigens are highly frequent (present in > 99.6% of individuals), 134 are less frequent (< 1%), and the others are polymorphic. These frequencies impact on transfusion compatibility.

The incidence of alloimmunization after transfusion ranges from 1% to 35% depending on population genetics and exposure history. Alloimmunization is more common in certain clinical settings, particularly when the donor and recipient are of different ethnicities. For example, patients with sickle cell disease (SCD) develop anti–red blood cell alloantibodies in 30% of cases when transfused with blood from Caucasian donors, but in only 6% of cases when transfused with blood from donors of African descent [3,4].

Serologic hemagglutination is the gold standard for red blood cell phenotyping, but it has limitations in the detection of rare antigens due to cost and labor constraints. Molecular genotyping made its appearance [5,6] with the first methods such as Polymerase Chain Reaction, Matrix-Assisted Laser Desorption/Ionization - Time Of Flight Mass Spectrometry, and DNA chips. However, these tools only detect known polymorphisms, limiting their application. Next-generation sequencing (NGS), used for HLA typing, is transforming blood group genotyping with the emergence of commercial solutions [7]. It enables high-throughput analysis of the entire gene. While powerful, NGS requires advanced bioinformatics and data storage capacity. Third-generation platforms, such as *Oxford Nanopore Technologies* (ONT), offer long-read sequencing that resolves complex genomic regions and allows for haplotype phasing, essential for accurate blood group determination [8,9]. These technologies open the way for rapid identification of compatible donors not only on red cell antigens but also on HPA, HNA, and HLA antigens, which will represent significant advances in the prevention of alloimmunization [10].

The immunogenicity of red blood cell antigens is variable between and within blood group systems. The most immunogenic systems are RH, KEL, FY, JK, and MNS, with RH1 (D) being the most immunogenic in European populations, followed by KEL1. Other antigens have variable immunogenic potential. In clinical practice, approximately 50% of alloantibodies are directed against RH antigens, 40% against KEL1 and FY1, and only 5% against other specificities [11].

Classic human leukocyte antigen and red blood cell alloimmunization

For several years, numerous studies have consistently shown a correlation between the presence of specific classical HLA alleles and the development of anti-RBC alloimmunization (Table 1).

Anti-D

Although older publications show no significant correlation between the HLA typing of 'good responders' to RH1 (D) antigen and 'poor responders' [12], many more current studies have already shown that HLA-DRB1*15 confers to susceptibility to D alloimmunization [13]. This association was supported by an anti-D immune response could be induced by HLA-DRB1*15 transgenic mice and by the overrepresentation of HLA-DRB1*15:01 allele in D-negative donors who have produced D antibodies in response to exposure to D-positive RBC units [14]. Other authors show a link between HLA-DRB1*01 and anti-D immunization [15].

Anti-E

Few studies have shown that alloimmunization with the E antigen is associated with HLA-DRB1*09 in European populations [15,16]. This association is confirmed in China with high frequencies [17–19]. The

Table 1

Classic HLA and RBC alloimmunization.

Anti-RBC antibody	Risk	Protective	Ref
Anti-D	DRB1*01		[15,16]
	DRB1*15		
	DQB1*06		
Anti-E	DRB1*09		[15–18]
Anti-K	DRB1*11		[20,23]
	DRB1*13		[15,20]
		DRB1*07	[23]
Anti-Fya	DRB1*04		[15,20,25]
	DRB1*15		[15,25,26]
	DRB1*01		[15]
	DQB1*06		[26]
	DQB1*03		
		DRB1*03	[25,26]
		DRB1*07	[25]
		DRB1*13	[26]
		DQB1*02	[26]
Anti-Jka	DRB1*01		[15,27]
Anti-RBC antigen	DRB1*15		[33]
	DRB1*15:03		[32,40]
	C*06		[24]
	DQB1*03		[24]
	DRB1*11		[33,40]

DR9 molecule interacts with the sequence containing the polymorphic determinants of the E antigen with high affinity [18].

Anti-Kell

The *in silico* analysis using the TEPITOPE algorithm or NetMHCII software highlighted that the K antigen had a high degree of histocompatibility promiscuity, explaining the high frequency of anti-K also found in all populations [20,21]. Thus, one anchor peptide L194-202G was able to bind to almost all DRB1 molecules in single responders with anti-K. In this case, the polymophism of Kell (193M), which is a residue before this peptide, seems to play the role of flanking residue, which allows better recognition of the antigen by the CD4+ T cells [22]. Interesting, DRB11 molecules seem to interact with anchor peptides close to the K antigen. Several studies showed that the frequency of HLA-DRB1*11 or HLA-DRB1*13 was significantly higher in K immunized patients [15,23,24]. The DRB1*11 and DRB1*13 alleles share an HLA-DRB1 gene sequence containing S in position 13, D in 70 and A in 74, and coding for the P4 pocket within the HLA-DR binding groove.

Anti-Fya

Retrospective studies in European populations have shown that patients alloimmunized against the Fya antigen have an increased frequency of HLA-DRB1*01, HLA-DRB1*04, and also HLA-DRB1*15 alleles [15,25,26]. More specifically, one study found an association with the HLA-DRB1*04:01 and HLA-DRB1*04:03 alleles, suggesting that some amino residues of the P4 pocket may be involved in binding to a Fya peptide [25]. One study found an association between anti-Fya immunization and HLA-DQB1*06, which is in fact in linkage disequilibrium with HLA-DRB1*15 [26]. Recently, the protective role of the HLA-DQB1*02 allele in Fya alloimmunization has been reported, which is consistent with other findings highlighting the protective role of HLA-DRB1*03 and HLA-DRB1*07 alleles in linkage disequilibrium with HLA-DQB1*02 [25,26].

Anti-Jk(a)

One French study showed that HLA-DRB1*01 was significantly more frequent in Jk(a) immunized patients, with a frequency of 50% of cases [27]. This association was confirmed [15].

The good responder

It is reasonable to assume that cumulative immunization against different blood group antigens may account for the risk associated with transfusion of multiple units of red blood cells. The likelihood of developing a new alloantibody increases significantly after a first RBC alloimmunization, with a reported 3.5-fold increased risk [28]. Among previously immunized patients, 21% developed an additional RBC antibody after further transfusions, with a median occurrence after two RBC units [29]. However, several studies suggest that this risk is not solely dependent on the number of units transfused but is more closely related to the immunologic profile of the patient, particularly the so-called 'good responder'. This profile is genetically determined, independent of the underlying disease or the patient's age, and relatively unrelated to the total number of transfusions received [28,30]. In addition to the D antigen, individuals carrying the HLA-DRB1*15 allele are predisposed to produce alloantibodies to other antigens, such as E and K, particularly following incompatible transfusions or pregnancy. HLA-DRB1*15 is often associated with multiresponders — patients who produce antibodies against multiple red blood cell antigens — and may confer a general susceptibility to antibody-mediated alloimmunity. Recent studies have confirmed that the frequency of the HLA-DRB1*15 allele is significantly higher in multiresponders compared to non-responders [15]. Notably, HLA-DRB1*15 is most commonly associated with anti-C and anti-D alloantibodies. In addition, compared to those who develop antibodies to a single antigen, individuals who develop multiple RBC alloantibodies are almost twice as likely to carry the HLA-DRB1*15 allele [15]. The association with HLA-DRB1*15 goes beyond alloimmunizing RBCs. It has also been associated with the development of multiple HLA antibodies, particularly in women exposed to transfusions and/or pregnancy [31]. Despite growing evidence, the mechanisms by which HLA-DRB1*15 contributes to alloimmunization against multiple antigens remain unclear.

Probably, the efficient antigen presentation is not the main explanation. *In silico* analysis showed that no restriction molecule alone can display all the antigens analyzed. However, HLA-DRB1*15 has specific physicochemical characteristics in residues 11P and 13R in the P4 pocket, which together with the influence of other residues can favor the response to various antigenic peptides [21].

The most persuasive hypothesis involves the pro-inflammatory profile associated with the HLA-DRB1*15 haplotype. HLA-DRB1*15-positive individuals produce antibodies causing more complement and inflammation-mediated damage than HLA-DRB1*15-negative individuals. Thus, cytokine profiles, *TNFA* –308G/A and *IL1B –511T* have been showed with susceptibility to RBC alloantibody formation in HLA-DRB1*15 SCD patients [13]. Finally, it has been suggested that HLA-DRB1*15 could be a surrogate marker of the risk of RBC alloimmunization, which supports the idea that HLA typing before transfusion could be helpful in reducing alloimmunization in chronically transfused patients [32,33].

Inflammation

Recent evidence showed that the inflammation status of the recipient is an important factor in the physiopathology of alloimmunization, notably in SCD [34,35]. In murine models of RBC transfusion, artificially induced inflammation enhanced humoral immunization, antigen presentation by dendritic cells, and more pronounced proliferative responses of CD4-positive T cells [36,37]. Recipient inflammation also transformed RBC alloimmune nonresponders into responders. While in the absence of inflammation, transfusion seems to result in tolerance to RBC antigens [38]. SCD is associated with a chronic inflammatory status [39] where nonspecific immune cells are activated by elevated levels of circulating hemoglobin and free heme released by hemolysis or by blood transfusions. The inflammatory phenotype of sickle cell disease is further characterized by high levels of acute-phase proteins and cytokines [40]. Genetic variability may influence the intensity and impact of this inflammation directly, particularly the severity of the disease and the occurrence of red blood cell alloimmunization. In addition, alloimmunized SCD patients showed reduced Treg and Breg activities, weakened immunoregulatory response, and intensification (increase) in T-cell response [41]. Interesting, few polymorphisms in genes involved in inflammation pathways, such as TRIM21, CD81, TLR1, TLR2, CTLA4, and FCGR2B, has been show associated with RBC alloantibody development [41,42].

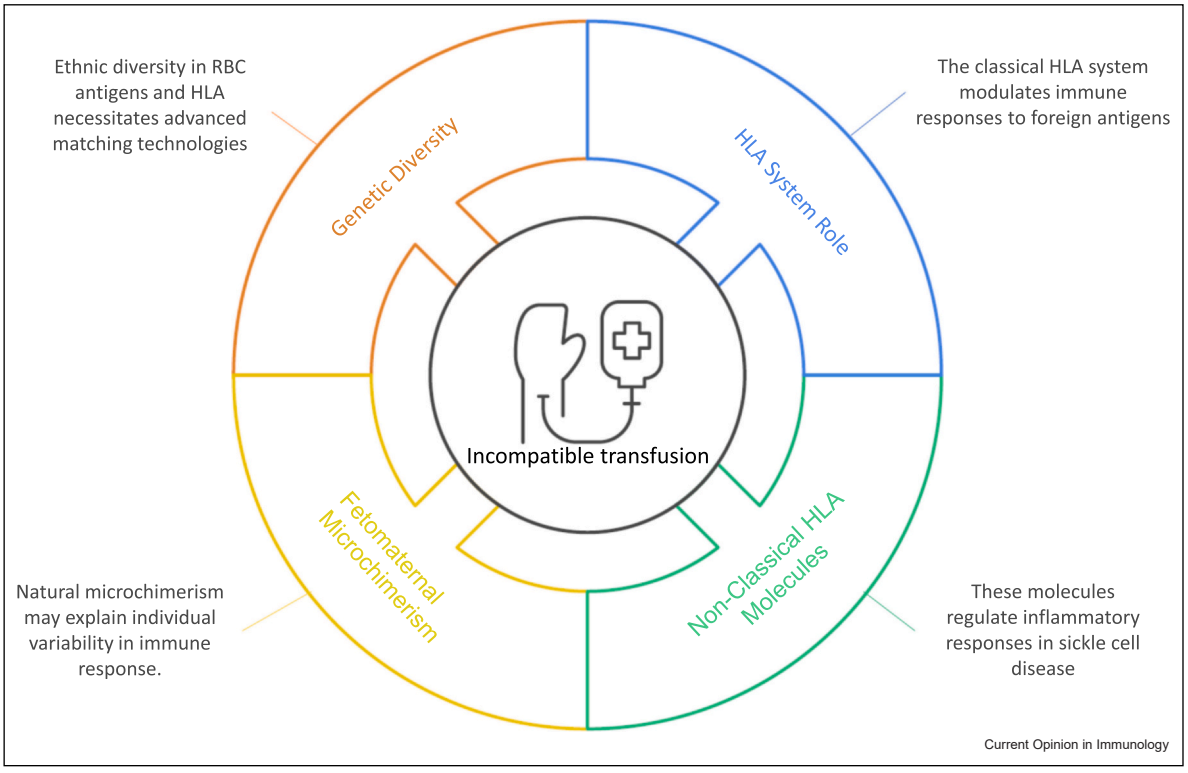
Nonclassical HLA

In this context, nonclassical HLA (HLA-G, HLA-E, and HLA-F) and their receptors (LILRB1, LILRB2, and KIR3DS1) could participate to inflammation levels in SCD and could influence the alloimmunization risk. Indeed, nonclassical HLA molecules play a major role in inducing tolerance during pregnancy but also in organ transplantations [43,44]. HLA-G, HLA-E, and HLA-F are expressed at the materno-fetal interface, whereas trophoblast lacks all other classical class I antigens except HLA-C. Their tolerogenic properties confer a peculiar interest in comprehension of the alloimmunization process during pregnancy and transfusions. Thus, HLA allo-immunization was reduced by certain HLA class Ib alleles (HLA-E*01:06, HLA-F*01:03, and haplotype HLA-G UTR4) during pregnancy [45]. HLA-G +3142C > G was more frequent among SCD patients who develop antibodies against antigens of blood group systems other than the Rh and Kell [46]. This polymorphism has already been associated with a worse prognosis for some clinical conditions such as auto-immune diseases, spontaneous abortion, or organ transplantation [47–49]. The authors concluded that (1) HLA-G molecule may take part in the alloimmunization process; (2) the immune pathways underlying the development of antibodies against high and low immunogenic RBC antigens are likely to be different. Similarly, nonclassical open reading frame in the FCGR2C gene (FCGR2C.nc-ORF) was strongly associated with a decreased alloimmunization risk, and this protective effect was strongest for exposure to antigens other than the immunogenic Rh or K antigens [50]. A recent study involving 37 adult SCD patients did not confirmed difference in frequency of allelic frequency of HLA-G and HLA-E genes in alloimmunised patients and non-alloimmunised patients. However, the authors show that alloimmunization in DICS patients is associated with HLA-F and LILRB1 genetic polymorphisms located in their regulatory region and associated with their protein expression levels [51]. HLA-F noncoding polymorphisms was previously associated with higher levels of HLA-F expression in both immune and nonimmune cell types, but the function of HLA-F in adaptative immune system is not well known [52]. Interestingly, the protective effect was statistically relevant only in the absence of the KIR3DS1 gene, suggesting that the interaction between KIR3DL1 and HLA-F may be important for immunomodulation in SCD patients. These discrepancies in the frequency of nonclassical HLA alleles require multicenter studies with larger numbers of patients with or without sickle cell disease. The impact of nonclassical HLA regulatory polymorphisms may be different depending on the intensity of immunogenicity of the RBC antigens (high or low immunogenicity) and the type of pathology transfused (sickle cell disease vs leukemia). Furthermore, it must be investigated in a broader alloimmunisation perspective, since alloimmunisation against HLA [53] was reported to be associated with RBC antibodies in multitransfused SCD patients.

Microchimerism

The bidirectional exchange of cells between the fetus and the mother that occurs during pregnancy creates what is known as maternal–fetal microchimerism. This microchimerism persists in hosts for decades after delivery. Thus,

Figure 1



Overview of risk factors involved in red blood cell alloimmunization.

maternal noninherited antigens (NIMA) expressed on maternal microchimeric cells are also present in the child [54]. The fetal immune system, exposed to maternal HLA molecules during pregnancy, is expected to develop a tolerogenic response to these molecules. This NIMA concept mainly concerns the HLA system in the outcome of hematopoietic stem cell transplantation and, more recently, in solid organ transplantation. It has been notably demonstrated a strong association of NIMA-matching with decreased risk for the development of acute GvHD in the context of various transplantation strategies. Recently, maternal grandmother cells have been observed in umbilical cord blood, confirming that pregnant mothers can transfer their mother's exchanged cells [55]. Theoretically, it could be assumed that an RHD heterozygous grandmother could reduce via the NIMA effect, the anti-D immunization rate of the pregnant D-negative mother, as NIMA could induce a state of low reactivity [56]. This theory needs to be tested, as does its possible extension to the 'non-responder' phenotype in red cell alloimmunization.

Conclusion

Although the risk factors for alloimmunization are still poorly understood, they appear to be multifactorial, involving immunological, genetic, and maternofetal microchimerism components (Figure 1). In fact, alloimmunization against red blood cell antigens results from an adaptive immune response modulated by genetic factors, particularly class II HLA alleles. Certain alleles, such as HLA-DRB1*15, are associated with a 'responder' profile, promoting antigen presentation and alloantibody production. The diversity of the HLA system contributes to the variability in immune responses, especially toward RH, KEL, FY, and JK antigens. Nonclassical HLA molecules (HLA-G, -E, -F) may also play a regulatory role by influencing mechanisms of tolerance and inflammation — an especially relevant consideration in chronic inflammatory contexts, such as sickle cell disease. Red cell group genotyping in conjunction with HLA genotyping will become important methods in the prevention of alloimmunization in transfused patients.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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