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Genetics of Transfusion Recipient Alloimmunization: Can Clues from Susceptibility to Autoimmunity Pave the Way?

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Summary
The search for genetic determinants of alloimmunization in sickle cell disease transfusion recipients was based on two premises: i) that polymorphisms responsible for stronger immune and/or inflammatory responses and hemoglobin β^S mutation were co-selected by malaria; and ii) that stronger responder status contributes to development of lupus. We found a marker of alloimmunization in the gene encoding for Ro52 protein, also known as Sjögren syndrome antigen 1 (SSA1) and TRIM21. Surprisingly, the nature of the association was opposite of that with lupus; the same variant of a polymorphism (rs660) that was associated with lupus incidence was also associated with induction of tolerance to red blood cell antigens during early childhood. The dual function of Ro52 can explain this apparent contradiction. We propose that other lupus/autoimmunity susceptibility loci may reveal roles of additional molecules in various aspects of alloimmunization induced by transfusion as well as during pregnancy.

Introduction

About 8% of African Americans are heterozygous carriers of hemoglobin S and 1/500 has sickle cell disease (SCD). In 1973, the average life span of a patient with SCD was 14 years. The development of comprehensive care has decreased early mortality and increased life expectancy to 50 years. Transfusion is a key component in the management of SCD patients [1], and its use has increased over time for prevention of stroke [2] and other complications.

RBC transfusion therapy is complicated by the development of antibodies specific for allelic (alloantibodies) or self (autoantibodies) RBC determinants. Alloantibodies are more frequent than autoantibodies, the clinical significance of which remain questionable. The presence of anti-RBC antibodies may cause delay in finding suitable blood for transfusion, which can result in life-threatening anemia. In addition, anti-RBC antibodies may cause delayed hemolytic transfusion reactions resembling sickle cell crises that can be lethal [3–5]. Finally, anti-HLA antibodies promoting rejection of hematopoietic cell grafts are more frequent in patients with anti-RBC antibodies [6]. Anti-RBC antibodies develop in 18–47% of patients with SCD [7–11], usually after receiving a small number of transfusions (responders; Rs), while other patients remain antibody-free (non-responders; NRs), despite extensive exposure to donor RBC antigens. RBC-specific antibodies make selection of RBC and assurance of cross-match compatibility extremely complicated. Further, transfusion of incompatible blood when no other options exist may result in increased hyper-hemolysis and poor in vivo survival of the transfused RBCs. The use of antigen-matched blood has been suggested to prevent alloimmunization, decrease the risk of delayed hemolytic transfusion reactions, and reduce morbidity in transfused SCD patients. This, however, has two drawbacks: i) utilizing antigen-matched blood for all patients, even if they are NRs; and ii) a lifetime commitment of ensuring antigen-matched blood, which is impractical for all Rs, given the cost and resources needed.

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Factors Influencing the (Non-)Responder Status

The rates of alloimmunization in SCD patients (18–47%) are considerably higher than those found in transfused patients without SCD (0.2–2.8%) [12–15]. This may be due to antigenic disparity, i.e., different blood group antigen distribution between predominantly Caucasian blood donors and SCD patients who are of African or African-Caribbean descent [16]. This concept is supported by reduced alloimmunization frequency in SCD patients in Saudi Arabia (13.7%), Uganda (6.1%), Egypt (21.4%), and Tunisia (16.6%) where blood donors and SCD patients are from similar ethnic background [17–20]. Even lower alloimmunization rates (2.6%) were noted in a Jamaican patient cohort [21], but might have been secondary to low number of units received (1–2 per patient). However, even these reduced rates are higher than the 'background' rate of 0.2–2.8%, suggesting that additional factor(s) may influence alloimmunization.

There are NR patients with documented multiple exposures to RBC antigens. So, what other factor may have a decisive influence on alloimmunization? Stochastic modeling suggested that a subgroup of transfusion recipients has genetically determined increased risk of alloimmunization [22]. Genetic factors controlling inflammatory responses are possible candidates, as the state of inflammation in recipients may activate the innate immune system and convert an inert or even a tolerogenic event into an immunogenic one [23, 24]. Indeed, in the SCD mouse model, recipient inflammation induced with poly (I:C) treatment augmented humoral immune response to transfused antigens [23]. However, not every form of inflammation promotes alloimmunization in mice, as lipopolysaccharide failed to induce the same effect as poly (I:C) [25]. Not surprisingly, elevated levels of cytokines are not markers for alloimmunization [26] and only some forms of pro-inflammatory events are associated with alloimmunization (Fasano et al. submitted).

Selection of High Responders in Africa

If inflammatory signals contribute to alloimmunization and SCD subjects have higher rates of alloimmunization, then individuals with SCD (or people of African descent, in general) should be prone developing stronger inflammatory and immune responses then other transfused subjects. This, indeed, appears to be the case, as SCD patients display increased inflammation and activation of innate immunity [27, 28] and increased levels of serum cytokines [29–32]. Evidence for higher rates of inflammatory conditions in African Americans in general also exists. Thus, incidence of lupus [33–35], asthma [36], hypertension [37], type 2 diabetes mellitus [38], obesity [39], necrotizing enterocolitis [40], and keloid formation [41] is higher in African Americans. In addition, African Americans display a significantly higher rate of arthritis and uveitis associated with Crohn's disease [42] and higher rates of acute graft rejection [43], and they require higher doses of immunosuppressive drugs post transplantation [44, 45]. Although such ethnic differences have traditionally been dismissed as a mix of environmental, social, cultural, and economic factors, evidence at the cellular and molecular level points to a contributing genetic component. Thus, African Americans have more robust cellular immune responses [46–48] and express higher levels of CD80 and CD86 co-stimulatory molecules [49, 50] compared to other ethnic groups. Furthermore, polymorphisms in immunomodulatory genes that favor expression of variants or levels of encoded molecules that promote stronger immune responses are more frequent in Africans/African Americans. These include multiple cytokine genes [51–53], CTLA-4 and PD1 co-stimulatory molecules [53], Duffy antigen receptor molecule [54] proposed to act as a 'chemokine sink' [55], and CD1d molecule [56] that presents antigens to NKT cells.

Why do Africans have stronger immune/inflammatory response? Although selective pressures of evolution on the human genome are very small [57, 58], there are several well-documented examples. Most of them involve selection by infectious agents, except for the intestinal lactase variant selected for amongst the dairy farmers [59]. Thus, sickle cell trait was one of the earliest recognized traits selected for. *HbβS* heterozygosity confers about 10-fold increase in protection against life-threatening forms of the malaria induced by *Plasmodium falciparum* [60]. Similar patterns of heterozygosity advantage are apparently conferred by other hemoglobinopathies as well as by glucose-6-phosphate dehydrogenase deficiency [61]. Distribution pattern of cystic fibrosis mutation (higher frequency in northwest than in the south east Europe) suggests that heterozygosity may have been protective against cholera [62]. Perhaps the most striking example of selection is the Duffy antigen receptor molecule which is absent from the RBCs in almost 100% West Africans and serves as a receptor for *Plasmodium vivax* [63].

In addition to the RBC antigens, malaria infection has also exerted pressure for the development of strong immune responses. Polymorphic variants in *HLA-B, HLA-DR, IL-4, CD40L, FcGR2A, TNF-α,* and genes encoding other molecules affecting immune responses are more frequent in defined populations with increased resistance to malaria [64]. We therefore reasoned that there may be other as yet undiscovered malaria-selected polymorphisms that promote stronger immune responsiveness, and that some of them are likely to be close to *Hbβ*. The neighboring immune response-modifying genetic markers are more likely to segregate with *HbβS* than those located further away on the same chromosome, or those located on other chromosomes.

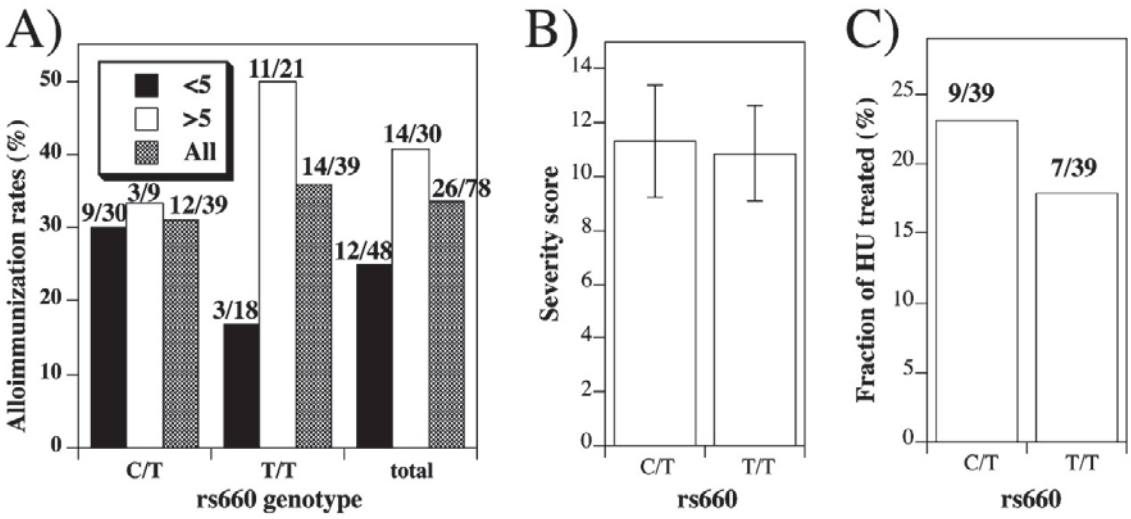

Fig. 1. Alloimmunization rates and rs660 genotype. **A** Frequency of alloimmunization in patients that received first transfusion before (closed bars) or after (open bars) the age of 5 (or all ages – shaded bars) in the function of rs660 genotype. The differences between alloimmunization rates in patients first transfused before or after the age of 5 were significant (Fisher's exact test) for T/T ($p = 0.043$), but not for C/T ($p = 1.00$) genotype, or for both groups together (0.195). Exact patient numbers are given above the bars. **B** Mean (± SE) SCD severity scores in patients with C/T or T/T genotype. Scores represent cumulative score B, calculated as described **C** Frequency of hydroxyurea treatment in patients with C/T or T/T genotype.

Polymorphism(s) in *Ro52* and Alloimmunization

Based on the above discussion we hypothesized that two linked malaria-protective polymorphisms were co-selected: the *HbβS* and an allele of a near-by gene, encoding a molecule with immunomodulatory function. The consequence of this co-selection would be stronger immune responses in *HbβS* homozygous individuals, reflected in a high incidence of antibody responses following transfusion. The near-by allele may not be the only locus favoring strong immune responses in SCD patients. Nevertheless, we felt that investigating this possibility would be an important step in understanding alloimmunization and, by extension, human immune responsiveness.

The best candidate gene in the vicinity of *Hbβ* on chromosome 11p15 was found 832 kb away. The gene encodes for Ro52 protein, also known as Sjögren syndrome antigen 1 (SSA1) and lately as tripartite motif (TRIM)21 [65]. Ro52 is best known as the target for antibodies that develop in lupus erythematosus and Sjögren syndrome, two autoantibody-mediated autoimmune diseases characterized by overall increased antibody production. Ro52 is part of an RNA-protein complex consisting of four small RNA molecules, Ro52 and two additional proteins, Ro60 and La [66, 67]. Mice deficient in Ro60 develop lupus [68] confirming that the molecule targeted by the autoantibody can have an active role in developing or protecting against lupus. Interestingly, *Ro52* gene harbors an SNP, designated rs660, with association with lupus in African Americans [69], but not in the Japanese population [70].

We therefore tested whether the rs660 genotype may be associated with alloimmunization in SCD. We recruited 83 patients of African American background homozygous for *hemoglobin S (HbS)* who received at least two ABO- and RhD-matched, cross-match-compatible leukodepleted RBC transfusions, documented by blood bank review. Overall distribution of rs660 alleles was unbalanced – 39 SCD patients were each of C/T and T/T, with only 5 patients with C/C genotype [71], similar to the frequencies previously observed in African Americans [70]. Consequently, comparisons were made between rs660C/T and rs660T/T patients. The frequency of alloimmunization in rs660C/T and rs660T/T patients was similar – 31% and 36%, respectively (fig. 1A). In addition, the markers of disease severity [72] (fig. 1B), the number of patients undergoing hydroxyurea treatment (fig. 1C), and the average total number of RBC transfusions received were indistinguishable ($p = 0.45$) in patients with rs660 C/T (84.3 ± 13.9) or T/T (101.2 ± 17.5) genotype (see also fig. 2D). Thus, rs660 does not associate with an overall rate of alloimmunization, or with indicators of severity of SCD.

Age at first transfusion is an important contributor to alloimmunization risk [73]. Mean age at first transfusion of SCD patients that developed at least one anti-RBC antibody was significantly lower in patients with rs660C/T than in patients with T/T genotype (fig. 2A; $p = 0.045$). In other words, relative to the rs660C/T patients, patients with rs660T/T genotype in general become alloimmunized if they are first exposed to RBC antigens late in life. The difference is not due to early initiation of transfusion in patients with the C/T genotype, since the average age of the first transfusion in antibody-negative patients was not significantly different (fig. 2A; $p = 0.1601$). When age at first transfusion was plotted for individual patients against the numbers of detected alloantibodies, it became clear that the age of 5 years represented the turning point (fig. 2B). The rate of alloimmunization in patients first

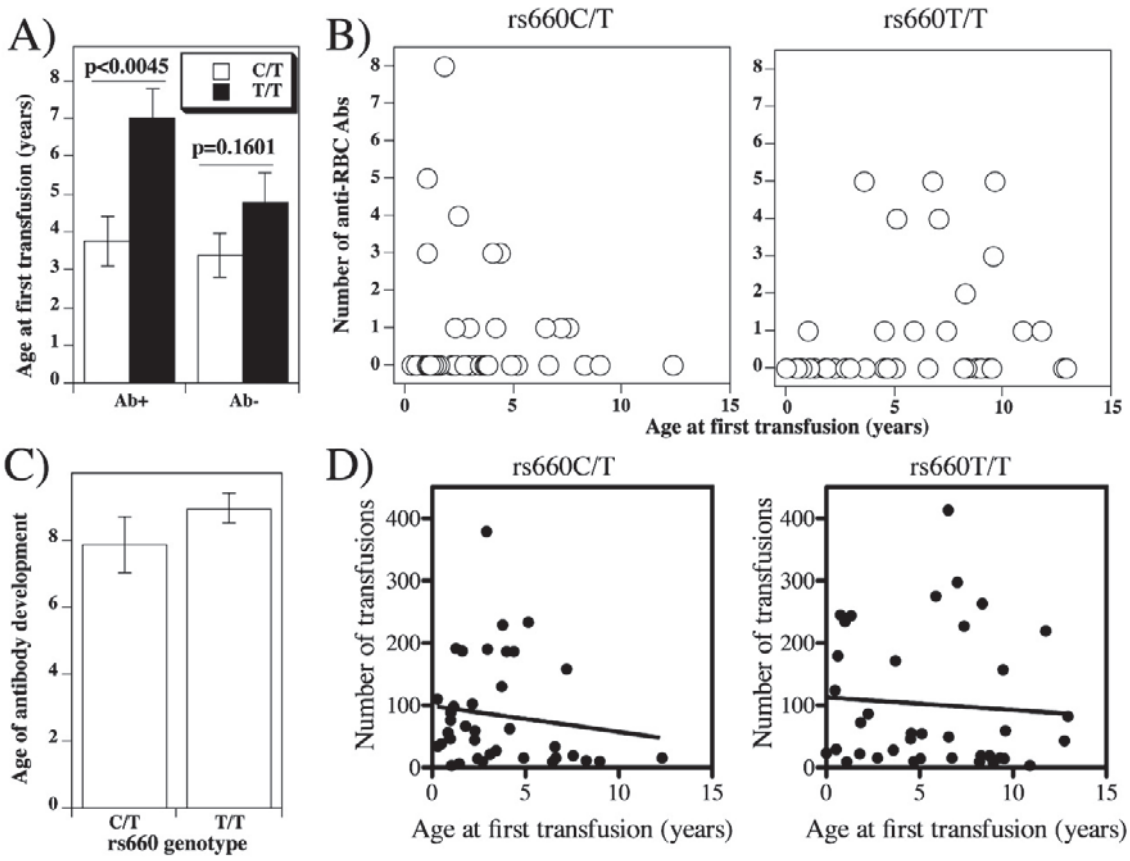

Fig. 2. Anti-RBC antibody production as a function of patient age at first transfusion. **A** Average age (± SE) of antibody positive or negative patients with rs660C/T or rs660T/T genotype when they received first transfusion. **B** The number of distinct anti-RBC antibodies detected in each patient in the function of the age at first transfusion of individual SCD patients with C/T (left) or T/T (right) genotype. **C** Average age (±SE) of patients with rs660C/T or rs660T/T genotype when individual antibodies were detected (differences are not significant; p = 0.3615). **D** Correlation between age at first transfusion with total number of transfusions in patients with rs660C/T or rs660T/T genotype. Correlation coefficients were: r = 0.1364 for rs660C/T and r = 0.0712 for rs660T/T patients (not significant in either case). Best-fit straight lines were obtained by linear regression analysis and are represented by the following formulas: y = –23.7 – 4.17x (rs660C/T) and y = 55.73 – 2.021x for rs660T/T. Deviations from zero were not significant (p = 0.414 for rs660C/T and p = 0.671 for rs660T/T genotype. Mean numbers of total transfusions received were 84.29 ± 13.92 for rs660C/T and 101.2 ± 17.47 for rs660T/T (p = 0.451).

transfused before 5 years of age was 30% if they were of C/T, and 17% if they were of T/T genotype (fig. 1A).

An important related issue is the patient age at antibody detection. Is the age at first transfusion an indicator of the age when antibodies develop? Age of subjects with C/T or T/T genotype when anti-RBC antibodies was detected was not significantly different (fig. 2C). This finding shows that patients with the C/T genotype are capable of producing anti-RBC antibodies after the age of 5, just like those with T/T genotype. In other words, the time it takes from the first RBC exposure to production of anti-RBC antibodies is much longer in patients with rs660C/T than in patients with rs660 T/T genotype. However, the latter respond mostly when RBCs transfusion is introduced beyond infancy and early childhood. Further, there is no correlation between total number of transfusions received and age at first transfusion in patients with either genotype (fig. 2D). Therefore, low alloimmunization rate in subjects with rs660T/T genotype when first transfused within the first 5 years of life suggests that they develop tolerance to RBCs more efficiently than rs660C/T subjects. The breakdown by antibody specificities suggests that tolerance is relatively equally inducible for several blood group antigens [71], excluding ABO and RhD antigens.

The term tolerance in immunology implies an active process induced by antigen. So, should the absence of antibody responses in SCD patients be designated ‘tolerance’, or perhaps a more passive term ‘non-responsiveness’ is better suited? The findings observed in patients with rs660C/T genotype clearly fit the ‘non-responsiveness’ designation: the patients developed antibodies to RBC transfusions after the age of 5 irrespective of whether they received transfusions before the age of 5. Thus, for this subset of patients exposure to RBC antigens during the early childhood did not alter the immune system responses to the same antigens later in life. However, administration of RBC transfusions before the age of 5 in patients with rs660T/T genotype clearly influenced non-responsiveness to RBC antigens after the age of 5. Although the exact timings of distinct RBC antigen exposures remain to be determined, it is evident that the ‘non-responsiveness’ in patients with rs660T/T genotype is induced, which in turn, is an operational definition of tolerance. Thus, we will in this review use the word ‘tolerance’, bearing in mind that it relates only to a subset of patients.

How can rs660 contribute to neonatal tolerance? Given that there appear to be differences in the levels of Ro52 expression in cell lines homozygous for rs660C and rs660T [71],

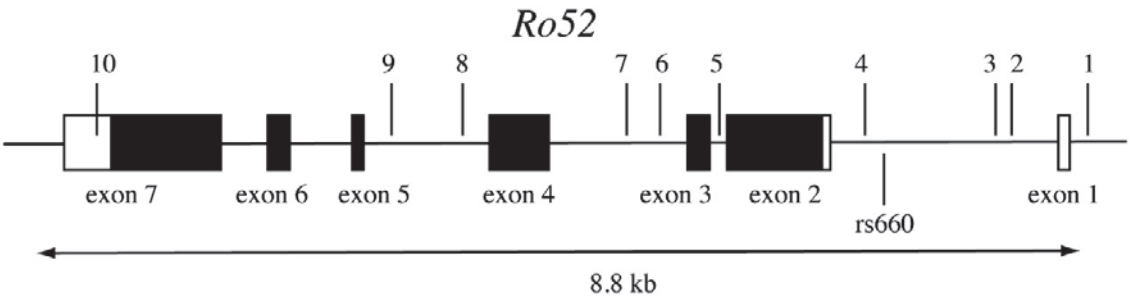

Fig. 3. Exon/intron structure of the *Ro52* gene and location of rs660. The coding and non-coding sequences are represented by closed and open rectangles, respectively. Indicated are the positions of rs660 below the line and ten arbitrarily chosen HapMap-validated SNPs above the line (1-rs1426378; 2-rs928914; 3-rs928915; 4-rs7947461; 5-rs926101; 6-rs2855142; 7-rs890419; 8- rs2554933; 9-rs2599586; 10-rs4144331).

one possibility is that rs660 is involved in enhancing or silencing the Ro52 expression. *Ro52* gene consists of seven exons (fig. 3) spanning 8.8 kb (*www.ncbi.nlm.nih.gov* accession number NC_000011). The rs660 polymorphic site is located about 600 bp upstream of the initiation codon [70] in the first intron [74]. Bioinformatics analysis using MatInspector software (*www.genomatix.de*) indicated that there may be a potential for differential binding of three transcription factors to the sequence around and containing the rs660 SNP. These factors include nuclear receptor subfamily 2, peroxisome proliferator-activated receptor and Myt1 C2HC zinc finger protein that can all potentially bind to rs660C, but not to rs660T. Interestingly, this pattern of binding, if confirmed, would be suggestive of silencing function of the surrounding DNA element. Another possibility is that rs660 is in linkage disequilibrium with another polymorphism in *Ro52* gene, or even outside the *Ro52*, that is directly involved in regulating Ro52 expression.

Extended Neonatal Tolerance Concept

The finding of tolerance in early childhood is not a new concept. The infants' immune system has long been thought to be prone to induction of tolerance, rather than immunity, as suggested by the classic neonatal tolerance experiments of Billinghamet al. [75]. They noted that tolerance to paternal antigens was acquired during pregnancy. These observations were inspired by Owen's studies of tolerance induction of antibody responses through in utero exposure to red blood cell alloantigens in cattle [76].

The concept of tolerance has been revisited frequently, and the original findings were confirmed in other species, including humans, and were extended beyond the neonatal into the early childhood period. In addition, most investigators now agree that neonates, infants, and children up to 5 years of age respond to antigens, but less efficiently than adults [77–80]. Examples include responses to malaria [80–82], factor VIII in patients with hemophilia [83], RBC antigens in patients with SCD [84] and thalassemia [84, 85], response to vaccines [80, 86], and the intensity of immune cell infiltration in tumors [87]. Further, prolonged replication of HBV and human CMV [88, 89], and more rapid progression to AIDS [90, 91] when infections occur in early life suggest less efficient pathogen clearance by the immune system.

What are the mechanism(s) for suboptimal responses in neonatal and early childhood period? At least a part of the answer may lie in the dynamics of T-cell receptor repertoire generation. T cells are generated in the thymus, and 1–2% of total thymocytes are each day exported to the periphery as mature T cells, referred to as recent thymic emigrants [92]. In young adult mice, about 20% of the peripheral T-cell repertoire represents recent thymic emigrants, while in the young mice (up to 3 weeks of age – corresponding to the early childhood in humans) this number is close to 100% [93]. The important aspect of recent thymic emigrants is their functional potential – they are less functionally competent than the long-term peripheral naïve resident T lymphocytes and require post-thymic maturation in the peripheral lymphoid organs to acquire full competency [94]. Therefore, a larger fraction of functionally less competent T cells repopulate peripheral lymphoid organs of neonates and young children. Hence, lower level responses are not surprising.

Another factor that may contribute to relatively weaker neonatal responses is the ontogeny of terminal deoxynucleotidyl transferase (TdT). This enzyme makes template-independent additions at the junctions of variable, diversity and joining junctions during T-cell receptor and immunoglobulin rearrangement. This is a critical step in generating the diversity of immune receptors – about 90–95% of the T-cell receptor diversity was attributed to TdT [95]. However, in most species neonatal T cells do not express TdT. In humans, TdT expression is first noticeable around weeks 18–19 [96]. The consequence of this pattern is that the neonatal T-cell receptor repertoire is suboptimal, with relatively lower avidity for antigens [97].

The function of B cells is also suboptimal in early childhood. Human neonatal B cells express lower levels of the co-stimulatory molecules CD40, CD80 and CD86, which decreases their interaction with T cells [98]. Further, marginal zone B cells are present in lower numbers and display lower levels of CD21 (also known as complement receptor 2) that

cripples their responses to thymus-independent 2 antigens (polysaccharides from encapsulated bacteria such as *Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae*) in children under 2 years of age [99–101]. This results in lower levels of IgG2 and IgG4 isotypes that reach the adult levels not until the age of 5–10 [102, 103].

Finally, innate pro-inflammatory immune responses are also attenuated during neonatal and early childhood period, whereas anti-inflammatory responses (e.g. IL-10 secretion) are enhanced [104]. Some suggested mechanisms include lower expression of TLR4, CD14, MyD88, and IRF5 [105–108]. Clearly, more research needs to be done on the functioning of the innate immune system in children, especially that related to TLR independent receptors like nucleotide oligomerization receptors (NOD) and retinoic acid-inducible gene I-like receptors (RLR) [109]. All in all, however, it is clear that both adaptive and innate functions of the immune system respond suboptimally during the neonatal period, and slowly progress towards adult levels during the early childhood.

Of Mice and Men

Our study implied a potential role for Ro52 in promoting the neonatal tolerance to RBC antigens. However, direct evidence was missing. To address this question Patel et al. [110] examined the role of Ro52 in a mouse model of alloimmunization using the *Ro52* knock-out mice. They transfused wild-type controls and Ro52 knock-outs with RBCs expressing the HOD transgene (a fusion molecule containing hen egg lyzozyme, portion of ovalbumin and human Duffy antigen receptor complex) and tested anti-HOD antibody production 2 weeks post transfusion. They found that juvenile mice transfused at 3 weeks of age failed to produce specific antibodies, while adult mice (10–16 weeks old) produced antibodies with maximal frequency, irrespective of their *Ro52* genotype. These results confirmed the suboptimal alloimmunization rates in young individuals, but according to the authors, did not support the role of Ro52 in promoting the early childhood tolerance.

So, what are the reasons for the discrepancy between the human and the mouse model? First, rs660 may be a marker of an adjacent functional gene other than Ro52. The association of rs660 with early childhood tolerance is through linkage disequilibrium with the causative genetic element that may, or may not lie, within the *Ro52* gene. If it lies outside, then negative result is expected if the Ro52 is knocked out.

Species differences in the immune system have been described that could account for distinctive experimental observations [111]. Although at this point no differences in the function of the human and mouse Ro52 were noted, it remains possible that human and mouse alloimmunization models are (partly) unique.

The impact of the complete absence of a protein (such is the case in the mouse knock-out model) may be different from the impact of changing the protein levels (which is the case in SCD patient cohort), even within the same species.

Another possible explanation may be related to the immunogenicity of RBC antigens. The HOD 586 amino acids long fusion protein contains three antigens foreign to the mouse immune system, whereas differences between RBC donors and recipients are in general less significant. The most drastic differences include 417 amino acids when RhD-negative subjects respond to RhD antigens (due to RhD matching; however, this occurrence is extremely rare in contemporary transfusion medicine), or 338 amino acids when Duffy-negative recipients respond to Duffy-positive transfusion. Mostly, however, the antigenic differences are much smaller and can sometimes be only one amino acid [112, 113]. Thus the strength of the antigenic stimulation in the mouse system may have over-ridden any relatively small impact of Ro52 that might become notable only after a more subtle antigenic challenge.

The apparent absence of the impact of the Ro52 in the mouse model may be viewed in an entirely different light if antibody levels are taken as a key measurement instead of alloimmunization rates. Thus, Patel et al. [110] noted that the levels of anti-HOD antibodies were significantly ($p = 0.02$) lower in Ro52 knock-out than in the wild-type mice. Perhaps, with a less immunogenic stimulation the lower response in Ro-52-deficient mice would be recognized as a reduced alloimmunization rate.

Finally, there are significant differences in the design between the mouse and human experimental models. Patients were exposed to RBC antigens during the early childhood period at least once, while the adult mice used in the study were exposed to the fusion antigen for the first time as adults (fig. 4). Thus, the mouse model does not replicate conditions observed in our study with SCD patients.

How Could Ro52 Induce Tolerance and Promote Lupus?

Assuming that rs660 association with both lupus and early childhood tolerance reflects a function of the Ro52 protein, we raise the following question: how can the same molecule be involved in apparently opposing outcomes? Ro52 can perform two opposing functions at the cellular level. Ro52 is an ubiquitin-conjugating E3 ligase [114] targeting various substrates for proteasome-mediated degradation. The best known substrates are IRF-3, IRF-5, IRF-7, and IRF-8 [115], hence the overall effect of Ro52 is inhibition of type I interferon production [116]. The overall anti-inflammatory role of Ro52 was confirmed by experiments in Ro52-deficient mice which mount excessive immune responses, characterized by production of autoantibodies and tissue pathology reminiscent of lupus [117].

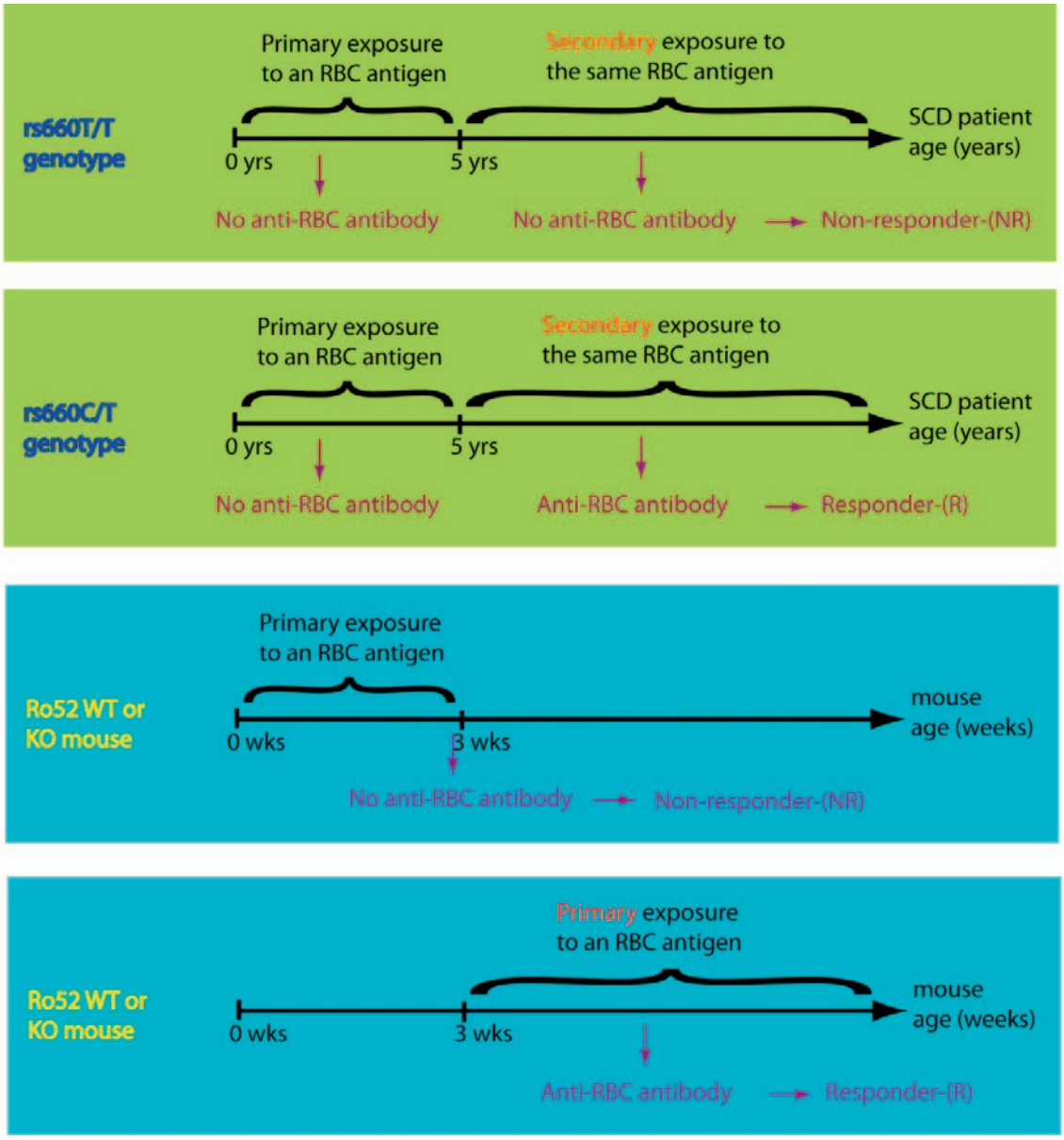

Fig. 4. Similarities and differences between the studies using experimental mice and human subjects.

However, Ro52 can also serve as an intracellular receptor for antigen-antibody complexes internalized via cell surface receptors that infectious agents use to enter the cells. This intracellular interaction results in activation of intracellular immune pathways, such as NF-κB, AP-1, IRF3, IRF5, and IRF7 [118]. This activates the production of pro-inflammatory cytokines, which promote resistance to viruses and intracellular bacteria [119]. Thus, depending on the context, Ro52 can have proinflammatory or anti-inflammatory actions. RBC antigens following transfusion are unlikely internalized as part of complexes with antibodies, hence anti-inflammatory function of Ro52 prevails. We would have to hypothesize that at least some antigen-antibody complexes that are abundantly formed in lupus are internalized, activating the intracellular immune reaction.

Conclusions and Future Directions

The present findings provide a proof of principle that lupus susceptibility locus rs660 may also be a marker of early childhood tolerance. There is a high possibility that both associations are mediated through the opposing functions of the same molecule – Ro52 – in regulating inflammation. In a similar manner, other lupus susceptibility loci [120], especially those that overlap with susceptibility to other autoimmune/inflammatory diseases [121], may be involved in promoting (anti-)inflammatory conditions favorable for producing antibodies and/or promoting tolerance following transfusion. Formal proof of linkage disequilibrium of rs660 with an element in *Ro52* gene remains to be established, as well as a more detailed cellular and molecular mechanism of early childhood tolerance.

The implications of determining the molecular and cellular basis of R-NR status in alloimmunization go beyond the transfusion medicine. Thus, although the backbone of therapy for solid organ transplantation is directed toward altering the function of T cells, it is becoming increasingly clear that T cells are responsible mainly for acute rejection, while the antibodies are the primary cause of chronic transplant rejection [122–124]. Furthermore, biopharmaceuticals such as factors VIII and IX, growth hormone, erythropoietin, and IFN-α can also induce antibodies that interfere with their therapeutic efficacy [125]. Finally, alloimmunization may occur naturally during pregnancy and cause a host of pathological conditions for the fetus as well as consequences for subsequent conception. The neonatal conditions linked to alloimmunization include fetal and neonatal alloimmune thrombocytopenia [126, 127], fetal and neonatal hemolytic anemia [128], alloimmune neonatal neutropenia [129], hydrops fetalis [130], neonatal hemochromatosis [131], biliary atresia [132], and neonatal glomerulopathy [133]. Alloimmunization was also proposed to at least partially explain implantation failure, recurrent pregnancy loss and pre-eclampsia/eclampsia [134, 135] as well as inflammatory lesions of the placental villi during pregnancy [136]. It is therefore clear that the lessons learned from genetics of lupus and autoimmunity in general may have a broader impact than initially thought.

Disclosure Statement

The authors declare no conflict of interest with the pharmaceutical industry or elsewhere.

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