



Red blood cell alloimmunization and sickle cell disease: a narrative review on antibody induction

Jeanne E. Hendrickson^{1,2}

¹Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT, USA; ²Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA

Correspondence to: Jeanne E. Hendrickson, MD. Department of Laboratory Medicine, 330 Cedar Street, CB 405, New Haven, CT 06520-8035, USA. Email: jeanne.hendrickson@yale.edu.

Abstract: The high prevalence of red blood cell (RBC) alloantibodies in people with sickle cell disease (SCD) cannot be debated. Why people with SCD are so likely to form RBC alloantibodies, however, remains poorly understood. Over the past decade, a better understanding of non-ABO blood group antigen variants has emerged; *RH* genetic diversity and the role this diversity plays in RBC alloimmunization is discussed elsewhere. Outside of antigen variants, the immune systems of people with SCD are known to be different than those of people without SCD. Some of these differences are due to effects of free heme, whereas others are impacted by hyposplenism. Descriptive studies of differences in white blood cell (WBC) subsets, platelet counts and function, and complement activation between people with SCD and race-matched controls exist. Studies comparing the immune systems of alloimmunized people with SCD to non-alloimmunized people with SCD to race-matched controls without SCD have uncovered differences in T-cell subsets, monocytes, Fc γ receptor polymorphisms, and responses to free heme. Studies in murine models have documented the role that recipient inflammation plays in RBC alloantibody formation, with human studies reporting a similar association. Murine studies have also reported the importance of type 1 interferon (IFN α/β), known to play a pivotal role in autoimmunity, in RBC alloantibody formation. The goal of this manuscript is to review existing data on factors influencing RBC alloantibody induction in people with SCD with a focus on inflammation and other immune system considerations, from the bench to the bedside.

Keywords: Alloimmunization; red blood cells (RBC); sickle cell disease (SCD); inflammation

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Introduction

People living with sickle cell disease (SCD) have the highest prevalence of red blood cell (RBC) alloimmunization of any studied population (1). Up to 40–50% of transfused people with SCD form RBC alloantibodies over their lifetimes (2–4), compared to fewer than 5% of the “general” transfused population (2,5). Potential reasons for this prevalence rate in people with SCD include a relatively high lifetime RBC transfusion burden, *RH* genetic diversity, and immune system considerations, among others. However, this prevalence is higher than that observed in other frequently transfused patient populations, including those with thalassemia major (6) or myelodysplasia (7).

RBC alloantibodies may be clinically significant in transfusion and pregnancy situations, potentially leading to hemolytic reactions or hemolytic disease of the fetus and newborn. Aside from hemolytic risks, these antibodies may make locating compatible RBC units for future transfusion difficult and at times impossible. Notably, RBC alloantibodies in people with SCD have been shown to be associated with decreased overall survival (8); related morbidity/mortality is likely under-reported (9). Besides forming RBC alloantibodies, people with SCD also readily form RBC autoantibodies as well as HLA alloantibodies (10). RBC alloantibody evanescence, or the disappearance of antibodies below a threshold detectable by the transfusion

service, makes future RBC transfusion particularly dangerous as a seemingly compatible RBC unit may result in a delayed hemolytic reaction (11). Emerging literature suggests such evanescence may be more common in people with SCD than in others (12). A complication of delayed hemolytic transfusion reactions that occurs at particularly high frequency in people with SCD is bystander hemolysis, or the destruction of self-RBCs; this complication is reviewed separately.

The goal of this manuscript is to review existing data on factors influencing RBC alloantibody induction in people with SCD with a focus on inflammation and other immune system considerations, from the bench to the bedside. This article is presented in accordance with the narrative review checklist (available at <http://dx.doi.org/10.21037/aob-2020-scd-01>).

General immune system considerations in SCD: a broad overview

SCD impacts many aspects of the immune system, from innate to adaptive immunity. Outside of transfusion medicine, the most recognized consequence of immune dysregulation in SCD is an increased risk of infection; infection has historically been a leading cause of morbidity and mortality world-wide in people with SCD (13). Along these same lines, responses to vaccines appear to be less sustained in people with SCD (14-17). Although hyposplenism presumably impacts the risk of infection as well as vaccine responses, it is also likely that alterations in white blood cell (WBC) subsets (18), platelets, RBCs, and complement are involved to some extent. Elevated WBC counts were described decades ago in people living with SCD (19). Activated neutrophils (20) from people with SCD have been described to be associated with disease complications such as pain crises (21) and they also contribute to neutrophil extracellular traps (NETs) (22). Thrombocytosis in people with SCD contributes to the inflammatory milieu (23), with people with hemoglobin (Hgb) SS disease having higher platelet counts than those with sickle cell trait or those with Hgb AA (24-26). Further, people with SCD also have high levels of soluble CD40L (27) and baseline platelet activation (28-30). The generation of free heme from ongoing RBC breakdown activates the alternative pathway of complement (31,32) and increased levels of complement C3-C5 have been noted in people with SCD compared to controls (33).

Inflammation and RBC alloantibody induction in SCD: a broad overview

In addition to antigenic differences between donor RBCs and recipient RBCs, the inflammatory status of the recipient at the time of RBC exposure likely impacts to some extent whether a recipient may become alloimmunized or not. People transfused in their baseline states of health, for example, are thought to be less likely to become alloimmunized than people transfused in a state of inflammation (34). Having acute chest syndrome or a pain crisis at the time of a RBC transfusion is a risk factor for becoming alloimmunized (35), as is having a viral illness (36) or other inflammatory disorder (37,38). Whereas transfusion can be avoided in some inflammatory situations, in others (including acute chest syndrome) it is considered a first-line therapy (39). Given the short half-life of RBCs in people with SCD, for example, free heme is continuously being generated and thus transfusing around “chronic inflammation” associated with free heme is not possible. The impact of free heme on immune dysregulation has been reviewed by Yazdanbakhsh *et al.* (40), with potential effects on the antigen presenting cell/CD4+ T-cell axis.

Inflammation and RBC alloantibody induction in murine models

Murine models have allowed inflammation-related variables to be dissected in ways simply not feasible in humans. For example, murine models can be designed such that the only non-self antigen in a transfused RBC unit is the KEL glycoprotein, the human glycophorin A antigen, or the triple fusion protein HOD (hen egg lysozyme, ovalbumin, human Duffy^b). The KEL and HOD mice were generated using a B-globin promoter (41,42), whereas the hGPA mice were generated using a BAC construct (43). The toll-like receptor 3 agonist [poly (I:C)], a double stranded RNA that mimics viral-like inflammation, is the form of inflammation that most consistently increases RBC alloimmunization in murine models (44-48). In some models, recipient treatment with poly (I:C) takes animals that would otherwise not form RBC alloantibodies and turns them into alloimmunized responders; in other models, poly (I:C) increases the magnitude of the alloantibody responses. For example, C57BL/6 wild type recipients of murine RBCs expressing the KEL glycoprotein transfused in the presence of an adjuvant like poly (I:C) develop anti-

KEL glycoprotein alloantibodies within days, with IgM forming first and then IgG developing days later (44). These anti-KEL antibodies are clinically significant and result in hemolysis of incompatible RBCs (49) as well as hemolytic disease of the fetus and newborn (50). Over the past few years multiple different KEL donor models have been studied, with transfusion of RBCs from one strain requiring an adjuvant to lead to an alloantibody response (51) and with transfusion of RBCs from a different strain being able to generate a moderate antibody responses without an adjuvant but having a higher magnitude of a response with an adjuvant (41). Likewise, recipients of murine hGPA RBCs develop anti-hGPA alloantibodies if transfused in the presence of poly (I:C) (45) or CpG; these antibodies are also clinically significant and lead to hemolysis of incompatible RBCs (52). Finally, recipients of murine HOD RBCs develop anti-HOD alloantibodies, with recipients pretreated with poly (I:C) generating a higher magnitude of anti-HOD antibodies (53). Besides poly (I:C), other forms of inflammation have been shown to impact RBC alloimmunization in murine models. For example, the toll-like receptor 4 (TLR4) agonist and bacterial endotoxin-like stimulus lipopolysaccharide increases alloimmunization rates in one model (47). Additionally, the toll-like receptor 9 (TLR9) agonist CpG, when mixed in with RBCs to be transfused, has been described by Yu *et al.* to increase RBC alloimmunization to murine RBCs expressing the hGPA antigen (54,55).

Outside of transfusion medicine, type 1 interferon (e.g., IFN α/β) is an important regulator of antiviral immunity and autoimmune pathology, with signal transduction through the interferon receptor (IFNAR) resulting in the expression of numerous interferon-stimulated genes (ISGs) that inhibit viral replication and dissemination (56). IFN α/β has been implicated in the pathogenesis of multiple autoimmune diseases, including rheumatoid arthritis, dermatomyositis, scleroderma, system lupus erythematosus, and Sjögren's syndrome (57-61). Further, multiple studies have shown that IFN α/β promotes adjuvant-induced antibody responses to soluble antigens by increasing activation of dendritic cells and lymphocytes (62-64). As autoimmune diseases are also associated with high prevalence rates of RBC alloimmunization (2,38,65), Gibb *et al.* hypothesized that IFN α/β may play a role in RBC alloimmunization. In fact, treatment with exogenous type 1 IFN has a similar adjuvant effect as treatment with poly (I:C) (51), and animals lacking functional type 1 interferon receptors (IFNAR knock out animals) do not form RBC alloantibodies. Further, animals

that cannot readily generate IFN α/β (e.g. animals lacking interferon regulatory factor (IRF) 3/7 as well as those lacking the upstream poly (I:C) receptor mitochondrial antiviral signaling pathway) also do not become alloimmunized following poly (I:C) treatment. Thus, IFN α/β plays a critical role in the way that poly (I:C) enhances alloimmunization in the murine models studied to date. Recently, recipient influenza infection has also been shown to exert a similar effect as poly (I:C) on RBC alloantibody induction in a murine model (66) and recipient treatment with exogenous type 1 IFN (IFN α) has been shown to have a similar adjuvant effect as poly (I:C) treatment (51).

To date, only a single study has been published investigating RBC alloimmunization induction in murine models of SCD. RBCs expressing the HOD antigen, transfused into animals with SCD (Hgb SS), did not result in an increase in responsiveness or in the magnitude of responsiveness compared with those transfused into animals with Hgb AS or Hgb AA (67). Murine models of SCD, summarized by Lizarralde-Iragorri and Shet (68), are just that; as such, it is not entirely clear how to interpret these data in the context of human SCD.

Characteristic of cell subsets as related to alloimmunization status in SCD

T-cells

With the assumption that most RBC alloantibody responses are CD4+ T-cell dependent in humans, descriptive studies have evaluated overall T-cell subsets in people with SCD with or without RBC alloantibodies. In general, people with SCD have been reported to have a lower percentage of CD4+ T-cells of all WBCs compared to race-matched controls, given the relatively higher percentage of monocytes and neutrophils. However, absolute numbers of CD4+ T-cells tend to be high in people with SCD given baseline leukocytosis (18,69,70). RBC alloimmunized children with SCD have been reported to have a higher percentage of circulating memory CD4+ T-cells relative to naïve CD4+ T-cells compared to children without antibodies (4); these findings have been replicated in adults with SCD (71). Neither of these studies evaluated antigen specific T-cells, however. Another study reported a relatively larger percentage of central memory CD4+ T-cells in an RBC alloimmunized population with SCD compared to healthy controls but not compared to a non-alloimmunized population with SCD (72).

Circulating T-follicular helper (Tfh) or Tfh-like cells (73) presumably play a role in alloantibody induction, at least for T-cell dependent antigens. Studies in autoimmune disease have reported a larger percentage of “highly functional” Tfh-like cells, whereas other studies have focused on the imbalance between Tfh and regulatory T-cells (Tfr) (74). Somewhat surprisingly, one SCD study reported a higher percentage of Tfh cells expressing CXCR5 and PD1 in non-alloimmunized subjects with SCD compared to alloimmunized subjects (72) and another study found no difference between those circulating populations (71). On the other hand, a study reported the presence of TIGIT (the T-cell immunoreceptor with IgG and immunoreceptor tyrosine-based inhibitory domains) positive Tfh cells expressing higher levels of CD40L in alloimmunized subjects with SCD (75), with such cells known to provide potent B-cell help.

B-cells

Extensive studies of B-cells in people with SCD are lacking, though modest increases in B-cell percentages of WBCs in general have been reported compared to controls (70). One study reported that regulatory B-cells from alloimmunized people with SCD have an impaired ability to inhibit monocyte proinflammatory cytokine production (76). Loss of IgM-secreting CD27+IgM^{high}IgD^{low} memory B cells has also been described in people with SCD (18), leading one to ask whether this plays any role in the relatively rapid evanescence of RBC alloantibodies (12). Although the relevance to RBC alloimmunization is not clear, a study in mice with SCD has described defective B-1b and B-2 populations, suggesting that these findings might play a role in impaired immunity to the pneumococcal vaccine (77).

Monocytes and antigen presenting cells

Multiple studies have investigated the role that monocytes may play in RBC alloimmunization (as well as other complications of SCD). Work completed by Zhong *et al.* has found that monocytes from people with alloantibodies express lower levels of heme oxygenase 1 (HO-1) compared with those from people without alloantibodies (78). Further, dendritic cells from alloimmunized people with SCD have been reported to be relatively refractory to the effect of free heme to down-regulate the CD83 marker; such down-regulation decreases proinflammatory effector T-cells (79). This resistance to free heme has been reported to be

dependent on TLR4, with DCs from alloimmunized people with SCD having an impaired ability to inhibit NF-κB.

Given the role that monocytes play in immune responses, a recent study hypothesized that FcγR1 (CD64) expression on monocytes may be associated with RBC alloimmunization status in people with SCD. Contrary to the hypothesis, lower CD64 expression was observed on classical (CD64+CD14^{high}CD16^{low}) and intermediate circulating monocytes (CD64+CD14^{high}CD16^{high}) in alloimmunized people with SCD compared to non-alloimmunized people (80).

In murine models, dendritic cells have been shown to play a key role in alloimmune responses to transfused RBCs expressing model blood group antigens, with transient depletion of conventional dendritic cells abrogating T and B-cell responses (81). Whereas multiple types of splenic dendritic cells have been shown to phagocytose transfused RBCs, only bridging channel (33D1+) dendritic cells were shown to be required for RBC alloimmunization (81).

Neutrophils

Though not conventionally considered antigen presenting cells, neutrophils have recently been shown to phagocytose RBCs and then to acquire an antigen presenting cell phenotype (82,83). Neutrophils have also been studied in other autoimmune disease such as systemic lupus erythematosus (SLE) in relation to their contribution to disease in general. While dendritic cells are more traditionally known for type 1 IFN production, bone marrow neutrophils have been shown to be drivers of type 1 IFN production and activation in SLE (84) (a disease also associated with a high prevalence rate of RBC alloimmunization). In a recent publication, Hermand *et al.* reported that neutrophils from a small cohort of people with SCD had high expression of proteins belonging to the type 1 IFN response pathway (85). Serum levels of IFNα were found to be 10–1,000 fold higher in about half of all people with SCD compared to controls, with increases in interferon signaling proteins (ISG15, IFIT1, MX1, STAT1, and STAT2) reported even in people with a normal serum level of IFNα (85). The relationship of these findings to RBC alloimmunization status remains to be evaluated.

Platelets

Platelets, best known for their role in hemostasis and thrombosis, are increasingly being appreciated to

participate in innate and adaptive immunity (23,86-91). To date, however, the role of platelets in RBC alloantibody formation in the general population has not been considered beyond one case series investigating febrile reactions to transfused platelets and the role of that fever on subsequent RBC alloimmunization (92). Platelets in people with SCD were first described to be activated more than a quarter of a decade ago (30), and drugs that target P-selectin have shown recent success in mitigating painful crises (93). Although studies have shown higher levels of CD40L and CD62p on platelets from people with SCD than from controls (28,29), only one small study to date has considered the role that endogenous platelets in people with SCD may play in the high prevalence rate of RBC alloimmunization (94). One observation worthy of brief mention is that people on chronic RBC erythrocytapheresis have been described to form fewer new RBC alloantibodies than those on simple transfusion therapy (95,96), despite exposure to significantly more RBC donors. The erythrocytapheresis procedure itself transiently removes about 50% of circulating platelets, making one wonder if endogenous platelets do in fact play a role in alloimmunization in humans. Future studies in this area are awaited.

Microparticles

Extracellular vesicles, including microparticles, are a topic of interest in SCD. However, the potential role of microparticles in RBC alloantibody development is unclear to date. Nader *et al.* (97) and others (98,99) have reviewed the existing literature on microparticles and SCD. Generated primarily from RBCs and platelets, the number of microparticles is significantly higher in people with SCD compared with healthy controls, and these numbers increase further with increasing degrees of hemolysis and with vaso-occlusion. Microparticles can promote endothelial cell activation and can increase the adhesion of neutrophils to endothelial cells (99,100). Of note, hydroxyurea use has recently been shown to decrease phosphatidylserine expression and the pro-inflammatory properties of microparticles (99). Microparticles also activate complement (101). Future studies of microparticles as “biomarkers” or “bioeffectors” in SCD (99) are anxiously awaited.

Cytokines

Polymorphisms of tumor necrosis factor- α and interleukin-

1 β have been reported as being over-represented in alloimmunized compared to non-alloimmunized people with SCD living in Brazil (102). In addition, interleukin-6 receptor signaling has been shown to impact RBC alloimmunization in a murine model (103). Overall serum levels of multiple cytokines have not been correlated with a history of RBC alloimmunization in at least two studies of people with SCD (80,104); studies of serum cytokine profiles at the time of new antibody formation, though logistically difficult to coordinate, might be more informative.

Complement

Constitutive complement activation is present with SCD, with the alternative pathway shown to be chronically activated in SCD more than 35 years ago (105). People with SCD have increased levels of complement C3, C4, and C5 compared to healthy controls (33), as well as increased erythrocyte C3 binding (106). Sickled RBCs that are dense are thought to be particularly susceptible to C5b-9 mediated lysis (107). The triad of free heme, TLR4, and P-selectin expression on endothelial cells has recently been shown to facilitate complement deposition, and then to provide a feedback loop for additional alternative complement pathway activation (108). Hyperhemolysis-mediated activation of the alternative complement pathway was described in a child with SCD with recurrent delayed hemolytic transfusion reactions (109,110). To date, no connection between RBC alloimmunization in general and the degree of hemolysis or the severity of anemia at baseline have been described, however. The question that remains unanswered at this point is whether this constitutive alternative pathway complement activation plays a role in the induction of RBC alloantibodies in humans with SCD; studies in mice have shown that complement can regulate RBC alloantibody induction in the absence of recipient CD4+ T-cells (110,111).

Other pathways or cells of potential interest in humans with relevance to RBC alloimmunization

A customized single nucleotide polymorphism (SNP) panel was utilized to evaluate 700 sequence variants in a multi-center case-control study of people with SCD living in France and The Netherlands (112). The group did not find any large-effect SNPs associated with RBC alloimmunization, though 19 SNPs that were determined

to be moderately associated with RBC alloimmunization were identified in the secondary analysis. Of these, the authors concluded that rs5743618 in TLR1 was likely the most important risk factor for RBC alloimmunization of the SNPs studied, with a four-fold increased risk of alloimmunization per A-allele. A SNP in TANK (encoding the protein TRAF family member-associated NF-kappa-B activator) was also identified as being of interest. SNPs found to be associated with alloimmunization prevention included those in STAM (encoding a protein involved in downstream signaling of cytokine receptors including IL-2 and GM-CSF), STAT4, and IFNAR (112). A different group reported a regulatory locus on Chromosome 5 to be associated with RBC alloantibody formation (113), with the same group reporting no large-effect SNPs in a smaller study of alloimmunized and non-alloimmunized people with SCD (114).

Low affinity Fcγ receptors have been evaluated in the context of RBC alloimmunization, given the known role of these receptors in different autoimmune and alloimmune diseases. People with SCD living in Europe that had a particular polymorphism (the *FCGR2C*nc-ORF polymorphism) were reported to have a 3-fold lower risk for RBC alloimmunization compared to people with SCD without that non-classical haplotype (115). However, this association was strongest for antigens other than Rh and K, which are among the most immunogenic. Recently, an Fcγ receptor 2B haplotype (2B.4) was shown to predict a significantly increased risk of RBC alloimmunization in people with SCD living in Brazil (116). Beyond Fcγ receptors, polymorphisms in TRIM 21 (Ro52) (117) and CD81 (118) have also been implicated in RBC alloimmunization.

HLA

For an alloantibody to develop, a person presumably must be exposed to a non-self antigen and have an HLA binding motif capable of presenting at least a portion of that non-self antigen. Variants of HLA class II, especially at the DR loci, have been described to be associated with RBC alloimmunization. Described in more detail elsewhere, multiple different HLA types have been shown to be capable of presenting portions of studied RBC antigens (119-126). Some HLA-DRB1 types have also been found to be associated with the development of multiple RBC and HLA alloantibodies (126).

Evanescence

RBC alloimmunization prevalence is presumably significantly higher than what has been reported, due in part of the phenomenon of evanescence, or antibodies falling below the level of detection by traditional blood bank methodologies. As described earlier, at least one study has reported higher degrees of RBC alloantibody evanescence in people with SCD compared with those in the general population (12). Fragmented medical care at different hospitals in the United States without shared medical records further increases the potential dangers of antibody evanescence (127). Without a shared RBC alloantibody registry or transfusion medicine database (128), this will continue to be a risk to people in the United States.

In addition to increasing the risk of delayed hemolytic transfusion reactions, evanescent antibodies may also increase the risk of bystander hemolysis (or destruction of self RBCs). Reviewed elsewhere, bystander hemolysis is more likely to occur in people with SCD than in other patient populations and may be deadly (11). Case reports of the efficacy of eculizumab support a role of complement activation in bystander hemolysis (110,129).

Blood donor or donor unit considerations

This review has focused on transfusion recipient variables. It is possible, however, that blood donor or blood unit variables (beyond antigen expression alone) may play a role in alloimmunization. Blood donor variables to consider include any that could lead to RBC damage or premature RBC clearance, potentially including donor G6PD deficiency or sickle cell trait (130-132); standard of care for transfusion of patients with SCD includes selecting donor units negative for sickle cell trait. In addition to free heme, unit factors that could impact the recipient's immune system include residual WBCs, platelets, microparticles, cytokines, or other damage-associated molecular patterns (133-135). The storage duration of a RBC unit may also impact the recipient's immune response, through free heme exposure or through other pathways (136). Whether storage duration definitively impacts alloimmunization in people in general or with SCD remains to be determined (137-140).

How to prevent RBC alloimmunization?

This manuscript has described cells and pathways that

Increased	Altered	
Complement activation	B-cells	} More efficient RBC antigen processing and presentation?
Endothelial cell activation/neutrophil adhesion	Cytokine profiles	
Free heme	Fc γ receptor polymorphisms	
Microparticles (RBC and platelet-derived)	Memory and naïve CD4 T-cells	} More efficient antigen trafficking?
Monocytes	Monocytes expressing heme-oxygenase 1	
Neutrophils and extracellular traps	Regulatory T-cells	} More RBC allo or autoantibody production?
Platelets and activated platelets		
Soluble CD40L		
Type 1 interferon (IFN α/β)		




Figure 1 Changes in cell subsets, inflammatory mediators, and polymorphisms that have been reported in people with sickle cell disease. The contribution of most of these variables towards the development of RBC alloantibody production remains under investigation. RBC, red blood cell.

may contribute to RBC alloimmunization (*Figure 1*), but what can be done to prevent alloimmunization? The short response is that this manuscript has raised more questions than it will be able to provide answers to. Judicious transfusion remains the leading strategy to prevent RBC alloimmunization, though many times transfusion cannot be avoided. Matching for blood group antigens such as C/c, E/e, and K is recommended for people with SCD (39), and phenotype as well as genotype matching is discussed in more detail elsewhere. Suppression of antibody formation through medication use has not been studied extensively, but patients receiving steroids or chemotherapy for other indications are less likely to form new alloantibodies (141). Strategies to mitigate or even prevent delayed hemolytic transfusion reactions with bystander hemolysis are actively being studied (39,129,142).

Conclusions

Although much has been learned about factors that influence the induction of RBC alloantibodies in animal models and in humans over the past few decades, much remains to be learned. It is likely that many if not most RBC alloantibodies are never identified or reported; as such, studies looking to identify risk factors for alloantibody development are hampered by the phenomenon of evanescence. Future studies incorporating basic science findings with clinical observations will help to advance our knowledge of RBC alloantibody induction; a better

understanding is necessary for optimal resource utilization to aid with the development of novel strategies for antibody prevention.

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