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Lessons learned from mouse models of hemolytic transfusion reactions

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Abstract

Purpose of review—Hemolytic transfusion reactions (HTRs) are potentially fatal complications of blood transfusions. Many studies, primarily performed *in vitro*, have provided a great deal of insight into the initiating events of HTRs; however, it is not clear how they are modulated and how they combine to lead to one or more of the final common pathways. Recently developed mouse HTR models now make it possible to enhance our understanding of the pathogenesis of HTRs; this will allow for the rational design of specific therapies to prevent or ameliorate this serious complication in transfusion medicine.

Recent findings—Mouse models support the hypothesis that “cytokine storm” plays an important role in the pathogenesis of HTRs. Nitric oxide and endothelial cell dysfunction are also implicated in the pathophysiology of these reactions. In addition, the intriguing phenomenon of “antigen loss,” where antigen crosslinking by alloantibody leads to antigen removal rather than RBC clearance, has been modeled and explored. Finally, these mouse models were used to evaluate new therapeutic targets employing complement receptor 1 peptide homologues and the anti-macrophage agent, liposomal clodronate.

Summary—Models of HTRs are valuable for gaining a better understanding of the pathophysiology of these potentially fatal complications of blood transfusion. The participation of various inflammatory mediators was shown to play a role in these reactions *in vivo*. This knowledge will lead to novel treatment options.

Keywords

Hemolysis; Cytokines; Antigen loss; Hemolytic transfusion reaction

Introduction

HTRs can be categorized into those that are acute (typically IgM-mediated) or delayed (typically IgG-mediated). Hemolysis in IgM-mediated HTRs is initiated by IgM antibody binding to its cognate alloantigen on transfused RBCs, leading to complement activation, formation of the membrane attack complex, and intravascular hemolysis. This is most frequently due to the accidental transfusion of ABO incompatible RBCs and can result in shock, renal failure, disseminated intravascular coagulation (i.e. DIC), and death [1]. Although

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infrequent, the mortality rate is similar to the incidence of transfusion-transmitted HIV infection.

Clinically significant IgG-mediated HTRs are more common, but less severe, than IgM-HTRs, occurring in approximately 1 in 6,700 transfusions [2]. However, these can also produce major complications, including death [3,4]. As an example, highly alloimmunized sickle cell disease patients pose a special challenge; they can experience severe IgG-mediated HTRs that can precipitate acute crises or the hyperhemolysis syndrome [5,6]. IgG-mediated HTRs typically result from the transfusion of RBCs that are mismatched for a “minor” blood group antigen that was not identified by routine laboratory testing, often because the recipient had not yet developed a detectable immune response to the relevant antigen; alternatively, they can result from an anamnestic alloantibody response resulting from a prior transfusion. This type of HTR usually occurs 3-14 days post-transfusion, coinciding with increased levels of IgG antibodies recognizing the foreign antigen.

Although much is known about the proximal steps in HTRs (e.g. how antibodies bind to antigen, how complement is activated, how IgG-coated particles bind to Fc-gamma receptors (i.e. FcγRs) and are subsequently ingested, etc.), much less is known about the pathophysiology of the downstream events and the final common pathways (e.g. how intravascular or extravascular hemolysis leads to shock, renal failure, DIC, and death). In addition, it is not clear why some individuals experience severe HTRs, whereas others are mildly affected or unaffected. Finally, there currently is no specific therapy for HTRs, primarily because it is difficult to perform human studies due to the sporadic nature of HTRs.

This review will address the use of mouse models to advance our understanding of the possible fates of transfused incompatible RBCs and the pathophysiology of HTRs. Concepts regarding future uses of these mouse models will also be discussed. In addition, models of autoimmune hemolytic anemia (AIHA), although not representing alloantibody-mediated hemolysis, have identified issues relevant to studies of HTRs, and are thus included in this review.

Animal models of incompatible RBC transfusion

The use of animal models to study the immune response to incompatible RBC transfusions is not new. Many different types of animal models were used to study immune-mediated destruction of homologous or xenogeneic RBC and its sequelae [7-12]. However, each of these has problems. For example, although rabbits are inexpensive and easy to manipulate, there are relatively few genetic variants or well-characterized reagents available. In contrast, although non-human primates are probably the most appropriate to study for insights into the human situation, they are expensive, outbred, immunologically-relevant genetic variants are not available, and there are significant ethical issues.

Currently, murine models are the most useful because there are many pathophysiologically-relevant reagents (e.g. monoclonal antibodies, cytokines, etc.), transgenic mice, and knockout mice available to study the mechanisms underlying HTRs. Although murine RBC blood group systems were described previously (Ea1 – Ea10) [13-16], and can be used to model alloantibody-mediated HTRs [17,18], little is known about the biochemistry, immunology, or gene sequences of these mouse RBC antigens. Although some have transfused human RBCs into mice to study HTRs, human RBCs have twice the diameter of murine RBCs, they do not survive normally in mice [19,20], and the precise mechanism of clearance of these xenoantigen-expressing RBCs is unknown. This clearance is not primarily antibody mediated because human RBCs are still rapidly cleared in nonobese diabetic/severe combined immunodeficient mice [19]. As a result, these difficulties stimulated several groups to develop novel mouse models for studying of HTRs.

Mouse models of HTRs

Three new mouse models of incompatible transfusion have recently been described. Table I summarizes the advantages and disadvantages of each model along with other possible models that could be exploited in the future. These models are described in more detail below along with a brief discussion of mouse AIHA models.

Human Duffy transgenic model

Campbell-Lee et al. [21], utilizing transgenic mice expressing the human Duffy(b) antigen (i.e. Fy^b), were the first to describe a murine HTR model using a clinically relevant antigen that is involved in human HTRs. In this active immunization model, transfusion of RBCs from transgenic Fy^b mouse donors into wild-type recipients leads to the formation of IgM and IgG alloantibodies with specificity for Fy^b. Subsequent transfusion with Fy^b-transgenic blood into alloimmunized mice leads to ~70% clearance of these incompatible RBCs within 24 hours. In this model, mice transfused with incompatible RBCs develop pulmonary vascular endothelial dysfunction associated with a decrease in nitric oxide responsiveness and increased vasoconstrictor tone [22*], thus implying that nitric oxide has a role in the pathogenesis of HTRs.

Human glycophorin A transgenic model

Mice transgenic for human glycoprotein A (hGPA), which carries the clinically relevant human M and N blood group antigens, have been used to develop models of IgG- and IgM-mediated alloimmune hemolysis [23*]. In these models, RBCs from hGPA-transgenic mice are transfused into non-transgenic recipients passively immunized with purified IgG or IgM hGPA-specific monoclonal antibodies. Passive immunization allows for complete experimental control of variables such as antibody isotype, IgG subclass, and antibody concentration. For example, RBC survival progressively decreased with increasing concentrations of circulating monoclonal anti-hGPA antibody. In addition, although complement participates in IgG1-mediated HTRs, activating FcγRs play a dominant role in the clearance of hGPA-transgenic RBCs. In contrast, complement is more important than activating FcγRs in IgG3-mediated RBC clearance in this model, suggesting that IgG subclass and/or specificity plays a role in the mechanism by which RBCs are cleared. Finally, passive immunization with IgM anti-hGPA antibodies leads to rapid (i.e. 50% clearance within 5 minutes), complement-mediated intravascular hemolysis accompanied by gross hemoglobinuria.

In a subsequent paper [24**], the hypothesis that IgG-mediated HTRs induce cytokine storm *in vivo* was confirmed using this model and two IgG1 anti-hGPA monoclonal antibodies. Thus, two hours after initiation of an HTR, very high levels of the pro-inflammatory cytokines interleukin (IL)-6 and monocyte chemoattractant protein-1, and moderately elevated levels of tumor necrosis factor-α were detected; these all returned to baseline by 24 hours. No significant elevations of IL-10, IL-12, or interferon-γ were observed at any time point. Complement was not required for release of these cytokines, because similar profiles were observed when complement C3 knockout mice were used as transfusion recipients.

mHEL transgenic model

A less well-known outcome of opsonization of RBCs by antibody is the loss of antigen from the RBC surface without a loss in circulatory lifespan of the “antigen suppressed” RBCs. This phenomenon has been documented in human transfusion recipients for many clinically-relevant antigens [26]. Surprisingly, when RBCs from mice transgenic for a transmembrane form of hen egg lysozyme (i.e. mHEL) are transfused into wild-type C57BL/6 mice that were

actively immunized with HEL, these incompatible RBCs undergo “antigen loss” instead of clearance [26]. In addition, this antigen loss is dependent on the presence of an activating FcγR, but does not require the presence of the spleen. Thus, this model will be very useful in studying the detailed mechanisms responsible for this intriguing outcome of RBC incompatibility.

For example, this model is robust in that non-hemolytic antigen loss is not mouse strain specific [25**]. Interestingly, passive immunization with various anti-HEL monoclonal antibodies, which opsonize incompatible RBCs, do not individually result in an antigen loss. This provided the basis for pursuing rigorous studies of antigen loss using combinations of six different intact anti-HEL monoclonal antibodies and their corresponding F(ab')₂ fragments; this approach demonstrated that antibody binding to multiple distinct epitopes, which produces antigen crosslinking, is required for antigen loss. A subsequent short report [27*] demonstrated the effectiveness by which a secondary anti-IgG1 antibody could act as the crosslinker of an IgG1 anti-HEL monoclonal antibody, thereby confirming the importance of antigen crosslinking in the induction of antigen loss. This raises the interesting, but yet unproven, hypothesis that rheumatoid factor, a naturally occurring auto-anti-IgG, can influence whether RBC alloantibodies in humans induce antigen loss or clearance.

Murine AIHA models

There are several useful mouse models of AIHA. For example, the New Zealand black mouse strain is predisposed to develop AIHA at approximately 6 months of age, which is caused by the production of anti-RBC autoantibodies [45]. The antigen specificities of multiple monoclonal antibodies derived from these mice have been determined [46], and, when injected into other strains of mice, these purified monoclonal antibodies induce autoimmune hemolysis [39]. In this model, liposomal clodronate, a potent anti-macrophage agent, significantly improves RBC survival, and this benefit lasts for 1-2 weeks [39]. AIHA also spontaneously occurs in dogs and liposomal clodronate is effective in this large-animal model of AIHA [47]. It was also effective in preventing clearance of IgG-opsonized RBCs in normal dogs. These results suggest that liposomal clodronate is safe and can potentially improve outcomes in AIHA. In addition, pre-treatment of potential RBC transfusion recipients with liposomal clodronate may be a useful approach in cases where the transfusion of crossmatch-incompatible blood is unavoidable, such as in a multiply alloimmunized sickle cell disease patient when compatible units are unavailable.

Murine AIHA models also provided much insight into the differences in the pathogenicity of anti-RBC autoantibodies from different IgG subclasses, the mechanistic contributions of the various FcγR types, and the role of complement. The lessons learned from these AIHA models were recently reviewed [38] and these findings may also be applicable to the alloimmune setting.

Future directions

One of the many remaining mysteries in transfusion medicine is why an *in vivo* interaction between antigen and antibody can result in so many different clinical outcomes, ranging from clinically inapparent to death. The role of a patient's underlying illness can be explored by combining mouse models of HTRs with well-characterized mouse models of various diseases, including sickle cell disease, diabetes, sepsis, endotoxemia, and other models of acute and chronic inflammation. Studies into the mechanisms leading to alloimmunization to RBC antigens are also vital to our understanding of why some patients actively respond to allogeneic blood by producing alloantibodies, whereas others appear to ignore this stimulus. The role of concurrent inflammation in the development of alloimmunization is the subject of another review in this issue.

The ultimate goal of understanding the pathophysiology of the various outcomes of incompatible transfusion is to develop novel clinically-relevant therapeutics to prevent or ameliorate these reactions. Although there are certainly differences between mice and humans, mouse models will be important for pre-clinical testing of these therapies, such as the use of a mouse model to show that complement receptor 1 peptide homologues significantly prolong the survival of transfused incompatible human RBCs [48*].

Conclusion

As in humans, the transfusion of mice with crossmatch-incompatible RBCs does not always result in a HTR, and certain antigen/antibody combinations result in clinically insignificant reactions or even non-hemolytic antigen loss. Mouse models are beginning to unlock these mysteries and are shedding light on the pathophysiology of HTRs. These advancements will be used to develop novel therapies for treatment of these potentially fatal reactions.

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Abbreviations

HTRs, Hemolytic transfusion reactions; RBCs, Red blood cells; DIC, Disseminated intravascular coagulation; FcγR, Fc-gamma receptor; Fy, Duffy; hGPA, Human glycoprotein A; IL, Interleukin; HEL, Hen egg lysozyme; AIHA, Autoimmune hemolytic anemia.

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