



Commentary

Red blood cell antigen alloimmunization: Mysteries still unsolved



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It is generally more difficult to publish negative than positive scientific data, although everyone acknowledges how useful negative findings can be. This issue of *EBioMedicine* presents such negative results that are nevertheless valuable. Gibb et al. (Gibb et al., 2016) have addressed the question of the intracellular machinery pertaining to inflammation and its potential role in regulating alloimmunization to red blood cell (RBC) antigens. Gibb et al. attempted to test the role of mobilizing the inflammasome of innate immune cells in an experimental (mouse) model of alloimmunization. They sought to model real-life conditions of transfusion by providing stored RBC components (RBCCs). RBCC storage was previously shown to increase alloimmunization in the mouse, a model which simplifies the alloantigenic barriers. The relevance of old vs fresh RBCCs in humans is not yet ascertained with respect to medical outcomes (Martí-Carvajal et al., 2015), though there is common sense evidence that fresh cells may do better than old ones (Eikelboom et al., 2016). Studies investigating the effect of RBC storage time on alloimmunization in humans have given conflicting results, with a clear association observed in some settings, but no association in others.

In the current report, the authors hypothesized that damage-associated molecular patterns (DAMPs) share responsibility in inducing inflammation and subsequent alloimmunization. Storage for a limited period of time is indeed necessary to generate a safe blood component (BC) inventory, although it also results in the storage lesion (Delobel et al., 2016). To investigate their hypothesis, Gibb et al. focused on a major inflammasome molecule i.e. NLRP3, which is a member of the NOD-like receptor family that activates caspase-1 and triggers the release of IL-1 β and IL-18. Both of these pro-inflammatory cytokines fuel the inflammation linked-process of antigen presentation and the epitope specific T lymphocyte response to antigen presenting cells (APCs). The authors have used well-characterized inflammasome KO

mice, and elegantly proceeded with conventional dendritic cell (DC) depletion studies. They confirm the profound effect of storage on alloimmunization in this clear-cut model but also observe that NLRP3/caspase-1 is not required for the effect (Gibb et al., 2016).

While these data reject a relevant hypothesis that NLRP3/caspase-1 is required (e.g. negative data), they do not reject a potential involvement of NLRP3/caspase-1, due to the potential for redundant pathways that may rescue the phenomenon even if a major pathway is eliminated. It has to be understood that redundant pathways are natural safety measures, and are thus likely to be present in many systems.

Transfusion (and pregnancy)-induced immunization to blood cell antigens is the first adverse event after transfusion of cellular BCs, with frequency varying from 0.1% to 10% depending on the cohorts, the transfusion operation system and the hemovigilance and reporting system. In humans, because of the multiplicity of genetically independent blood group antigens, perfect matches between BCs' and the recipients' phenotypes are not practically possible. Alloimmunization may be extremely serious when patients present with pathologies requiring chronic transfusion, such as thalassemia major and sickle cell disease. It is estimated that even in settings where blood components are pre-storage leukoreduced to less than 10^6 residual cells, nearly 10% of sickle cell disease patients become immunized to RBC antigens other than RH:1 (D) antigen (Semple, 2004) (and nearly 30–50% when BCs are not leukoreduced). The cumulative production of multiple alloantibodies can render the recipient refractory to transfusion.

Despite these rates of alloimmunization, the vast majority of transfusion is tolerated in a manner such that no significant alloantibody is formed that compromises subsequent transfusion or complicates pregnancy. Immunological reasons for variant responses to antigen mismatched blood cells are not well understood. They are comprised of factors linked with: -i) donor characteristics (antigens vary in immunogenicity); -ii) BC characteristics (prestorage, leukoreduction, age of blood, plasma mitigation, Transfusion Immuno Modulation (TRIM)-related factors); -iii) recipients characteristics (genetic susceptibility, causal disease, associated treatment, and immunomodulatory or immunosuppressant drugs).

For several decades, alloimmunization has been ascribed solely to the immunogenicity of BC antigens. It was then acknowledged that systematic, prestorage, and stringent leukoreduction significantly reduce the frequency of alloimmunization (Semple, 2004). Meanwhile, interesting studies from experimental mouse systems indicated that

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complete leukoreduction was less effective at diminishing alloimmunization, suggesting some room for TRIM (Pavenski et al., 2012). The beneficial effect of leukoreduction on alloimmunization sheds light on the so-called indirect presentation by professional APCs to recipients' T-lymphocytes (Pavenski et al., 2012). Later still, a new paradigm in alloimmunization has been recognized. Immunized patients were no longer ascribed a status of “good responders” but rather as “good presenters”, as their HLA receptors preferentially present certain blood group antigen epitopes (Körmöcz and Mayr, 2014): as a matter of fact, this is an unfortunate selective (dis)advantage as compared to being a “good presenter” of infectious pathogen derived epitopes. This is a case of direct presentation (recipients' APCs present to their own T-lymphocytes). Data has now accumulated showing that inflammation is central to (allo)immunization (Hod, 2015); inflammation allows the recruitment of APCs, the creation of a cytokine/chemokine milieu (along with the activation of other Biological Response Modifiers [BRMs]). Pro-inflammatory BRMs are seminal to the success of antigen presentation, the dampening of tolerance, and the rescue of reactive T-lymphocyte apoptosis (Pietrosimone and Liu, 2015). Inflammation can be viewed as the consequence of the activation of innate immune cells detecting a series of danger signals through surface pattern-recognition receptors (PRRs) detecting DAMPs on allogeneic blood cells. Once activated, these sensors activate intracellular pathways that end up regulating gene expression; as a consequence, the cell sensor secretes specific pattern of BRMs (Pietrosimone and Liu, 2015).

Beyond providing insights allowing better handling of chronically anemic patients, one can contemplate the capacity of Nature to use tricks to distract external attempts to dampen alloimmunization. Transfusion with homologous BCs is unnatural and is sensed as foreign material and perceived as potentially dangerous by the innate immune system: such a response is indeed derived from a set of safety measures

present in the immune system to protect the body against foreign pathogens. This also indicates that measures to dampen the system may be sought—that would ideally “distract the distractors”, despite a likely difficulty in achieving this task.

Disclosure

The author declared no conflicts of interest.

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