



## Scientific Comment

# Red blood cell alloantibodies and autoantibodies: different presentation, same physiopathology<sup>☆</sup>

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Alloimmunization is one of the most relevant post-transfusion complications as it is associated with transfusion delays, hemolytic disease of fetus/newborn and hemolytic transfusion reactions, which can be fatal in some cases. The ability of developing red blood cell (RBC) alloantibodies is restricted to a specific group of blood recipients, namely 'immune responders', whose genetics and inflammation background favors the antigen-presenting event and strengthens the Th2 response. Interestingly, multiple cohorts of multi-transfused patients have revealed that the group of immune responders is also prone to the development of RBC autoantibodies, which correspond to approximately 8% of all identified antibodies.<sup>1</sup> In most cases, both alloantibodies and autoantibodies are due to RBC transfusions and the presence of autoantibodies is considered a risk factor for alloimmunization itself, marking the condition of immune responsiveness.<sup>2</sup>

In this issue of Hematology, Transfusion and Cell Therapy, do Valle-Neto et al. describe the alloimmunization profile of a cohort of multi-transfused patients from Minas Gerais, including both sickle cell disease (SCD) and non-SCD patients.<sup>3</sup> The group reported a significant prevalence of autoantibodies within the cohort (6.54%), which was much higher in the group of alloimmunized patients (29.16%) in comparison to the non-alloimmunized group (2.32%). This data elegantly reinforces previous evidence in the literature regarding the high frequency of RBC autoantibodies among alloimmunized patients under chronic transfusion therapy, and highlights

that both alloantibodies and autoantibodies are probably formed through similar paths of adaptive immune response.

Taking a close look at the physiopathology of RBC alloimmunization, it is no surprise to find a strong association between autoantibody and alloantibody development. B cells are the cornerstone of autoimmunity and are also key elements in the initiation of alloantibody production. Most of the genetic polymorphisms associated with the risk of post-transfusion antigen sensitization refer to molecules taking part in the antigen-presenting event, some of which have already been linked to a higher risk of autoimmune diseases and their associated autoantibodies.<sup>4</sup> Considering that post-transfusion RBC autoantibodies usually emerge after or concomitantly with alloimmunization, the hypothesis is that the immune response directed against transfused RBCs seems to expand to self-antigens.<sup>5</sup> Thus, an exacerbation of Th2 response plays a central role in both autoimmunization and alloimmunization triggered by transfusion.

The high frequency of autoantibodies among alloimmunized patients sheds light on an important, but still unsolved question concerning how clinically relevant these post-transfusion self-directed antibodies are. While some studies suggest they are quite benign, justifying occasionally mild hemolysis, there are reports of very severe post-transfusion autoimmune hemolysis related to this mechanism.<sup>5</sup> In these dramatic situations, diagnosing the self-directed nature of erythroid destruction may be challeng-

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ing, especially because it occurs in previously alloimmunized blood recipients and may resemble hyperhemolysis. Taking into consideration all the evidence related to the physiopathology of post-transfusion RBC autoantibodies, the good news is: preventing alloimmunization also prevents autoimmunization. The enemy to be defeated is still the same.

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### Conflicts of interest

The authors declare no conflicts of interest.

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