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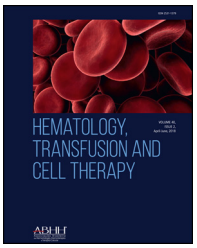

Scientific Comment

A future without human leukocyte antigens?☆

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Platelet transfusion is an essential supportive therapy for patients with hemato-oncological disorders as many of them present with thrombocytopenia and bleeding. Platelet refractoriness, defined as the lack of adequate post-transfusion platelet count increment, remains a challenge in the management of platelet transfusion dependent patients. The majority of refractory cases have nonimmune causes and include infection/sepsis, fever, splenomegaly, use of antibiotics and even storage conditions.[1] Immune causes comprise ABO incompatibility, antibodies against class I human leukocyte antigens (HLA) (mostly HLA-A and HLAB), and antibodies against human platelet antigens (HPA). In hematology/oncology patients, platelet refractoriness has been reported in 7–34% of cases.[2]

The transfusion needs of patients with immune platelet refractoriness triggers a series of processes that include the identification of the immune cause, the search for and notification of compatible donors in a genotyped donor bank, the donation of the actual blood product and finally its release and availability for use. These are lengthy procedures, which are costly and often unsuccessful. On the other hand, we have the refractory patient, bleeding or at imminent risk of bleeding, where urgency and agility are essential. These are two dissonant situations attempting to converge on the same goal. In this regard, despite the few studies that rigorously assess bleeding in patients requiring cross-matched platelet support, the refractory state is associated with increased mortality.[3]

Thus, the development of technologies that aim to optimize the availability of the blood product as described by Ferreira et al. who report the use of a tool which identifies potential donors even with a limited database of genotyped donors, are extremely welcome in transfusion medicine and are important weapons in the management of these cases.[4] Nevertheless, processing constraints remain and are the basis for potentially fatal situations.

Against this background, solutions must be obtained. The *ex vivo* production of HLA-free transfusion products represents an alternative.

In 1995, Choi et al. described the possibility of generating $CD34^+$ hematopoietic progenitor cell (HPC)-derived platelets *in vitro* using thrombopoietin (TPO) and a specific cytokine cocktail.[5] Since then, many groups have investigated the feasibility of producing platelets from umbilical cord blood, peripheral blood progenitor cells, bone marrow progenitor cells and human embryonic stem cells.[6–10]

Recently, the feasibility of generating mature functional megakaryocytes from human pluripotent stem cells has been demonstrated.[11,12] Human induced pluripotent stem cells (iPSCs) represent an unlimited cell source for the production of blood products. Additionally, iPSC-based blood pharming approaches have been combined with genome editing technology.[13] Despite the fact that all of these approaches hold a great potential in the field of transfusion, the probable HLA-incompatibility with the recipient remains a major hurdle to their future application. To circumvent this problem there is an interesting proposal to generate platelets by using transcription activator-like effector nuclease (TALEN)-mediated targeted disruption of the β2 microglobulin gene.

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☆ See paper by Ferreira MG et al. on pages 298–304.

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Knocking out β2M expression eliminates HLA class I cell-surface expression, which is thought to be a major cause of platelet refractoriness.[2] Figueiredo et al. demonstrated a stable reduction of HLA class I surface expression obtained by using a combination of lentiviral gene transfer and RNA interference technology to target the conserved β2m molecule which is an essential part of dimeric HLA class I molecules.[9] By this methodology, the authors revealed the capacity of HLA-silenced megakaryocytes, such as platelets, to escape anti-HLA antibody-mediated cytotoxicity.

Altogether, these studies show the feasibility of pharming producing engineered platelets *in vitro* with advantageous features that promote their maximal therapeutic efficacy. The next challenge in this field is the production of clinically relevant platelet numbers. Indeed, some research groups have already shown the feasibility of producing platelets in bioreactors.[14,15] Their use for the large-scale production of universal platelets may open a new horizon in the field of transfusion medicine.

Conflicts of interest

The author declares no conflicts of interest.

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