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blood donors does not significantly affect posttransfusion RBC recovery or donor cognitive function. Nonetheless, it remains unclear if there are specific subsets of donors for whom iron repletion might improve blood product quality or cognition. Indeed, female subjects, but not male subjects, who received iron repletion showed a statistically significant increase in posttransfusion RBC recovery. Moreover, the study excluded individuals 16 to 18 years old, who comprise >10% of donors in the United States and are at higher risk of developing iron deficiency and related complications.[9,10] Such individuals may be particularly vulnerable to iron deficiency due to ongoing neurological development where the consequences of iron deficiency may not be acutely manifest, but instead become apparent at much later time points postdonation. Identification of individuals at highest risk of morbidity due to iron deficiency could help guide donor-specific recommendations for iron repletion, changes in the eligible age range, and alterations in donation frequency. Although these additional questions remain, the present results provide important guidance on the impact of iron replacement for iron-deficient blood donors and suggest that the overall quality of the subsequently donated unit and the cognitive performance of the donor remain largely unaffected by iron replacement.

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REFERENCES

1. Hod E, Brittenham GM, Bitan ZC, et al. A randomized trial of blood donor iron repletion on red cell quality for transfusion and donor cognition and well-being. *Blood.* 2022;140(25):2730-2739.
2. Skouge E. Klinische und experimentelle Untersuchungen uber das Serumeisen. Videnskabsadkademien (Oslo) Skrifter. *Mat. Natv. Kl. Bd 1.* 1939;7:1-173.
3. Skold E, Waldenstrom J. Hamoglobin- och serumjarnvarden hos blodgivare. Ett bidrag till den s. k. blodningsanarniens patogenes. *Svenska Lak.tidn.* 1940;37:1359.
4. Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation a randomized clinical trial. *J Am Med Assoc.* 2015;313(6):575-583.
5. Kiss JE, Vassallo RR. How do we manage iron deficiency after blood donation? *Br J Haematol.* 2018;181(5):590-603.
6. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet.* 1996;348(9033):992-996.
7. Szczepiorkowski Z, Hopkins T. Updated Strategies to Limit or Prevent Iron Deficiency in Blood Donors, Association Bulletin #17-02. Accessed 2017.https://www.aabb.org/docs/default-source/default-documentlibrary/resources/association-bulletins/ab17-02.pdf?sfvrsn=55d7caaf_4
8. Keller P, von Kanel R, Hincapi CA, et al. The effects of intravenous iron supplementation on fatigue and general health in non-anemic blood donors with iron deficiency: a randomized placebo-controlled superiority trial. *Sci Rep.* 2020;10(1):14219.
9. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics.* 2001;107(6):1381-1386.
10. Spencer BR. Iron depletion in adult and teenage blood donors prevalence, clinical impact, and options for mitigation. *Hematol Oncol Clin North Am.* 2019;33(5):781-796.

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TRANSPLANTATION

Comment on Kong et al, page 2740

Chronic GVHD on the move

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In this issue of *Blood*, Kong et al present an additional pathophysiologic link between autoimmune diseases and chronic graft-versus-host disease (GVHD).[1] They demonstrate that peripheral T helper (Tph) cells and tissue-resident T helper (Trh) cells not only are clonally related but also are able to traffic between peripheral blood and target organs of chronic GVHD.

Recent progress has been made in treating chronic GVHD, and understanding of its highly complex pathophysiology is increasing. Despite these advances, this autoimmune-like clinical condition, with its diverse manifestations, remains an obstacle to successful allogeneic hematopoietic cell transplantation (allo-HCT), due to its impact on quality of life, morbidity, and mortality. In fact, the incidence of chronic GVHD has increased, owing to the increasing age of the patient population, the increased use of unrelated donors, and a lower level of treatment-related mortality.[2] In approximately half the patients with chronic GVHD, only 1 or 2 organs are involved, but many patients have multiorgan involvement, which can occur simultaneously or as sequential manifestations over the years. The particular organs that become involved, and whether flares of chronic GVHD occur, are largely unexplained and cannot be predicted clinically.

One critical insight is that chronic GVHD is not a single entity caused by a distinct immunopathologic mechanism; rather, its manifestations are mediated by several acute and chronic inflammatory pathways, as well as by dysregulated immunity leading to aberrant tissue repair, fibrosis, and immune dysfunction.[3,4] In contrast to acute GVHD, which is typically caused by postthymic donor T cells, chronic GVHD cannot be attributed to just one cell population. Even nascent, stem cell–derived T cells that have undergone selection in the host's thymus may cause autoreactivity, as thymic and lymphoid tissues can be damaged by transplant conditioning and/or acute GVHD. Similarly, B cells and plasma cells can produce autoantibodies, resulting in chronic GVHD that clinically resembles antibody-mediated autoimmune diseases. The modeling and study of such highly complex, pathologic events, either in preclinical mouse models or by use of primary human samples, remain challenging, and only a few have achieved success in this endeavor.

Defu Zeng and his group are among the researchers who have made significant contributions to a better understanding of the pathophysiology of GVHD. They recently reported that following allo-HCT,

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extrafollicular $CD44^{hi}CD62L^{lo}$ P-selectin glycoprotein ligand-1$(PSGL1)^{lo}CD4^{+}$ T (Tfh) cells differentiate into Trh cells with high expression of CD69, CXCR6, and purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7) in an IL-6R/Stat3-dependent manner. These Trh cells can form lymphoid aggregates in non-lymphoid GVHD target tissues, and interact with and provide help to B cells via the T-cell receptor–major histocompatibility complex (TCR-MHC) complex and programmed cell death protein 1 (PD-1) and programmed cell death ligand 2 (PD-L2), thereby promoting their differentiation into plasma cells producing IgG autoantibodies.[5] The current study builds on this previous work, studying the role of $CXCR5^{-}PD\text{-}1^{hi}$ extrafollicular Tph cells, which have been found in multiple autoimmune diseases. In contrast to Tfh cells ($CXCR5^{+}PD\text{-}1^{+}$), which help regulate antibody production and are decreased in patients and mice with chronic GVHD, extrafollicular Tph cells are expanded in autoimmune disease and, as reported here, also in murine and human chronic GVHD. In a well-established chronic GVHD mouse model, the absence of Tfh cells was confirmed and a marked expansion of Tph cells in the blood was documented. Organ infiltrates of lymphoid clusters comprised of Trh cells were found and were seen to be surrounded by collagen deposition. Tph and Trh cells share certain phenotypic and functional features, including the secretion of IL-21. In fact, Trh cells isolated from GVHD target organs and adoptively transferred into secondary recipients were detectable in GVHD target organs and in the blood, indicating that Trh cells can become Tph cells. Conversely, Tph cells were isolated and transferred into secondary recipients, in whom they also were detectable in GVHD target tissues, confirming that Tph cells can become Trh cells. Finally, Kong et al were able to demonstrate that a clonal relationship exists between the 2 T helper populations in the GVHD organs and the blood, using T-cell receptor sequencing. These experiments were validated by analysis of corresponding cell populations in allo-HCT-recipients, in whom moderate and severe chronic GVHD were associated with a significant reduction of Tfh cells and an expansion of Tph cells in the peripheral blood, resulting in augmented memory B cell differentiation and production of IgG via IL-21.

In patients, chronic GVHD often modulates over the course of several years. The condition can come to a standstill, or even improve, under treatment, but it can become active again at any time, and often does so following infection and other yet-to-be-identfied triggers. Recurrence of GVHD can both affect previously involved organs and involve new locations. The study of Kong et al provides a scientific explanation for this remarkable behavior. Migrating and trafficking pathogenic donor T cells residing in target organs initiate immunologic disease progression, resulting in pathogenic autoantibodies produced by activated B cells and plasma cells. Via the blood, they can reach other tissues and extend the reach of the disease. The roles of peripheral and Trh cells in exerting antileukemic effects and preventing disease recurrence need to be determined.

These findings are of clinical importance, as an understanding of the pathophysiology of a condition is a prerequisite for developing targeted, efficient treatment. Moreover, the data suggest that measurement of Tph cells may be used as a surrogate marker and an indicator of disease activity in organs affected by GVHD. As serial tissue sampling is not practical in clinical practice, a simple blood draw could provide the necessary information to allow optimal control of drug-based immunosuppression, thereby improving the outcomes of transplant recipients.

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REFERENCES

1. Kong X, Wu X, Wang B, et al. Trafficking between clonally related peripheral T-helper cells and tissue-resident T-helper cells in chronic GVHD. *Blood*. 2022;140(25):2740-2753.
2. Arai S, Arora M, Wang T, et al. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2015;21(2):266-274.
3. Cooke KR, Luznik L, Sarantopoulos S, et al. The biology of chronic graft-versus-host disease: a task force report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2017;23(2):211-234.
4. Socie G, Kean LS, Zeiser R, Blazar BR. Insights from integrating clinical and preclinical studies advance understanding of graft-versus-host disease. *J Clin Invest*. 2021;131(12):e149296.
5. Kong X, Zeng D, Wu X, et al. Tissue-resident PSGL1loCD4+ T cells promote B cell differentiation and chronic graft-versus-host disease-associated autoimmunity. *J Clin Invest*. 2021;131(1):e135468.

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