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# T follicular helper cells in transplantation: specialized helpers turned rogue

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Organ transplantation represents the treatment of choice for end-stage organ failiure associated diseases. Despite significant advances in medicine, well organized networks of organ sharing and distribution, and availability of novel and more potent immunosuppressive regimens, long-term outcomes after organ transplantation remain suboptimal, with an average of only 50% allograft survival by 10 years.[1] Allograft rejection is 1 important etiology of allograft failure, and consists of multi-layered cellular and/or humoral immunologic injuries against the allograft. The presence of donor-specific anti-HLA antibodies (DSA) in transplant recipients has recently emerged as a significant biomarker of poor allograft outcomes.[2] For example, approximately 30% of highly sensitized kidney transplant recipients present with significant serum titers of DSA post-Tx that correlate with increased risk of antibody-mediated rejections (ABMR) and, later on, with higher incidence of chronic rejection and allograft failure.

DSA are isotype switched, complement binding IgG antibodies directed against HLA molecules, and depend on $CD4^+$ T cell help to B cells for their generation. Among $CD4^+$ T cells, the recently discovered follicular helper T cells ($T_{FH}$) are recognized to be the subset of cells specialized in the cognate control of the magnitude and quality of antigen-specific B cell physiologic antibody responses after bacterial or viral infections, and vaccination.[3,4] In addition, $T_{FH}$ proved pivotal to pathogenic antibody responses in autoimmunity.[3,4] $T_{FH}$ cells are demonstrated to participate to the germinal center (GC) formation in the secondary lymphatic organs, where they provide critical help to B lymphocytes to differentiate into memory B cells, long-lived plasma cells, as well as to generate extra-follicular plasmablasts, and thus critical to the production of high-affinity IgG responses. $T_{FH}$ cells are characterized by the (i) expression of Bcl-6, the transcriptional repressor factor responsible for $T_{FH}$ development (ii) the expression of CXCR5, a chemokine receptor that drives $T_{FH}$ cells towards $CXCL13^+$ B cells in follicles (iii) the coexpression of costimulatory/coinhibitory molecules ICOS, CD40L and PD-1 (iv) production of IL-21.[3,4] Moreover, the $T_{FH}$ cell activity seems to be tightly modulated by regulatory T cells ($T_{REG}$), which may further control the size and output of the antibody responses.[5] Another important advance in the field of $T_{FH}$ cell research was the recent identification and characterization of human

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circulating $CXCR5^+CD4^+$ $T_{FH}$ cells in peripheral blood, ideal surrogate cells to monitor $T_{FH}$ cell activity (i.e. Ab responses) postvaccination or in patients with chronic antibody-mediated diseases.[6,7] Circulating $T_{FH}$ represent approximately 20% of peripheral blood memory $CD4^+$ T cells, are functionally heterogeneous and are comprised of Th1-$T_{FH}$, Th2-$T_{FH}$ and Th17-$T_{FH}$ subsets generated in response to distinct environmental cues at priming.[4] Interestingly, despite all these advances in knowledge, the direct contribution of $T_{FH}$ cells to alloimmunity, and specifically to DSA development leading to ABMR has not been totally understood in the field of organ transplantation, and therefore many aspects remain to be elucidated.

In this issue of Transplantation, Walters and Vinuesa[8] provide a comprehensive overview on the $T_{FH}$ cell biology, discuss the available literature on $T_{FH}$ cell research in transplantation, and highlight the progress and limitations in the field. They further discuss therapeutic possibilities for in vivo targeting $T_{FH}$ cell activity, in the attempt of disrupting DSA formation, mitigating or eliminating ABMR, and thus improving long-term allograft survival.

First, the journey of naïve $CD4^+$T cell differentiation towards the GC-$T_{FH}$ cell fate starts in the secondary lymphatic organs, and it is a complex multistep and multi-factorial process orchestrated by positive or negative checkpoints involving multiple transcriptional regulators, co-stimulatory and coinhibitory receptors, $T_{REG}$ and cytokines. Notably, many of these checkpoints have been considered targets of therapeutic intervention to disrupt $T_{FH}$ cell activity and their subsequent participation to pathogenic antibody formation. Second, preGC committed $T_{FH}$ cells may enter circulation where they can be readily detected, or may infiltrate the disease-target organ, creating tertiary lymphatic organ-like structures. Three subsets of circulating memory $T_{FH}$ cells with distinct abilities to stimulate naive and memory B cell differentiation and/or antibody production have been identified in humans. More importantly, alterations in $T_{FH}$ cell number, phenotype and function may correlate with antibody levels and/or disease activity, making them good surrogate cells to study antibody responses in healthy or in patients with chronic antibody-mediated diseases.

Third, transplantation research using small animal models confirmed that B cell production of high affinity allo-antibodies requires $T_{FH}$ cell help and the indirect pathway of alloantigen recognition. Moreover, IL-21, CD40 and ICOS proved critical for high affinity DSA generation, or ABMR development. Studies on $T_{FH}$ cells from transplant recipients, while very limited, identified $T_{FH}$ cells increase in circulation during recall humoral alloreactivity posttransplantation, and confirmed in vitro their ability to induce B cell differentiation and IgG production in an IL-21 dependent manner.[9] Detection of tertiary lymphatic organs-like formation in renal allograft biopsies was associated with IL-$21^+T_{FH}$ cells presence close to B cells infiltrates undergoing somatic hyper-mutation and isotype switching. These infiltrates were reported to correlate to acute and/or chronic ABMR occurence.[9,10] Disrupting the obvious chemokine-, costimulatory- and cytokine-pathways checkpoints proved efficient in targeting of $T_{FH}$ cells and humoral immunity, as shown by murine or nonhuman primate models of autoimmunity and transplantation. However, correspondent human trials are currently scarce and yet inconclusive.

Overall, given the importance of $T_{FH}$ cells to DSA generation and ABMR, these cells should be regarded as the next target of immunotherapy to prevent poor long-term allograft outcomes in organ transplantation. However, critical issues still remain to be further addressed: what $T_{FH}$ cell subsets are implicated in DSA generation and/or ABMR; what is the best approach to monitor $T_{FH}$ cell activity and their response to treatment; what checkpoints should be targeted; whether $T_{FH}$ cell *de novo* priming and memory reactivation are equally sensitive to therapy; and how this targeted therapy may fit in the current puzzle of standard of care immunosuppression.

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## Abbreviations

| | |
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| **ABMR** | antibody mediated rejection |
| **Bcl-6** | B cell lymphoma 6 |
| **CXCR5** | CXC chemokine receptor 5 |
| **CXCL13** | CXC chemokine ligand 13 |
| **DSA** | donor specific anti-HLA antibodies |
| **GC** | germinal center |
| **ICOS** | inducible T cell costimulator |
| **IgG** | immunoglobulin G |
| **PD-1** | programmed cell death receptor 1 |
| **$T_{FH}$** | T follicular helper cells |
| **$T_{REG}$** | regulatory T cells |

## References

1. Organ procurement and transplantation network and scientific registry of transplant recipients 2010 data report. Am J Transplant. 2012; 12:1–156.
2. Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. New Engl J Med. 2013; 369(13):1215–1226. [PubMed: 24066742]
3. Crotty S. T follicular helper cell differentiation, function, and roles in disease. Immunity. 2014; 41(4):529–42. [PubMed: 25367570]
4. Ueno H, Banchereau J, Vinuesa CG. Pathophysiology of T follicular helper cells in humans and mice. Nat Immunol. 2015; 16(2):142–52. [PubMed: 25594465]
5. Aloulou M, Carr EJ, Gador M, et al. Follicular regulatory T cells can be specific for the immunizing antigen and derive from naive T cells. Nat Commun. 2016; 7:10579.doi: 10.1038/ncomms10579 [PubMed: 26818004]
6. Bentebibel SE, Lopez S, Obermoser G, et al. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. Sci Transl Med. 2013; 5(176):176.

7. Morita R, Schmitt N, Bentebibel SE, et al. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. Immunity. 2011; 34(1):108–121. [PubMed: 21215658]

8. Walters GD, Vinuesa CG. T follicular helper cells in transplantation. Transplantation. 2016 IN PRESS - THIS ISSUE.

9. de Graav GN, Dieterich M, Hesselink DA, et al. Follicular T helper cells and humoral reactivity in kidney transplant patients. Clin Exp Immunol. 2015; 180(2):329–340. [PubMed: 25557528]

10. Deteix C, Attuil-Audenis V, Duthey A, et al. Intragraft Th17 infiltrate promotes lymphoid neogenesis and hastens clinical chronic rejection. J Immunol. 2010; 184(9):5344–5351. [PubMed: 20357253]