Editorial: The Spectrum of Treg Subsets in Transplantation: Immune Regulation and Tolerance Induction

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Editorial on the Research Topic

The Spectrum of Treg Subsets in Transplantation: Immune Regulation and Tolerance Induction

Immune regulation that maintains immune homeostasis is an important part of the immune system. In this regard, regulatory T cells (Tregs) play crucial roles (1). Thymic Tregs (tTregs) express distinct T cell receptor (TCR) repertoires compared to effector T cells but, similar to effector T cells, also consist of naïve, central memory, and effector memory subsets, either in a resting or activated state, with a higher expression of functional regulatory molecules. Thymic Tregs are divided into 3 subpopulations, including naïve/resting Tregs (CD4+, CD45RA+, CD25+, and Foxp3lo), activated/memory Tregs (CD4+, CD45RA−, CD25++, and Foxp3hi), and non-Tregs (CD4+, CD45RA−, CD25+, and Foxp3lo) subpopulations. However, other markers such as HLA-DR and CD45RA may discriminate Tregs with high suppressive activity from other subpopulations. Activated Tregs have more suppressive activity than other Treg subpopulations, and there is a direct association between their frequencies and better allograft status (2, 3). Some studies have reported that activated Tregs are associated with operational tolerance or better allograft status (3–5). However, some other studies have reported inconsistent results. This may be due to the different study settings and strategies in determining Tregs (Aly et al.). Accordingly, in-depth analyses of Treg counts, subsets, and functionality in transplantation lead to a better understanding of their impact on the posttransplant course and allow more personalized immunosuppression treatments.

To evaluate the capacity or threshold of inflammation on the alloimmune response, Cross et al. cultured both activated endothelial cells (aECs) and highly aECs (haECs) separately with allogeneic peripheral blood mononuclear cells (PBMCs); haECs need a high inflammatory condition to be established. *In vitro* analyses showed that the co-culture of aECs and PBMCs was associated with higher activated and naïve Treg differentiations compared to the co-culture of haECs and PBMCs. This suggests that controlling inflammation early after transplantation may improve the immunoregulatory capacity of transplant patients through the increase of activated Tregs. To control inflammation early after transplantation, we need to control innate immune activation. Innate immune activation occurs within 24–48 h after transplantation, in which neutrophils and

macrophages recognize endogenous danger signals (known as damage-associated molecular patterns). Consequently, innate immunity facilitates adaptive immune activation through efficient cytokine production and the increase of dendritic cell (DC) capacity to activate T cells (6).

MicroRNAs (miRNAs) are other factors that may improve the immunoregulatory capacity of transplant patients. In a seminal study, Yuan et al. showed the protective role of miR-223 in the transplantation outcome. miR-223 *via* inhibition of *IRAK1* reduces nuclear factor-κB (NF-κB) signaling, polarizes DCs into tolerogenic DCs, and reduces the expression of major histocompatibility complex class II and co-stimulatory molecules on the DC surface. Such DCs can reduce the T cell response, induce the Treg differentiation, and prolong the allograft survival time (7).

Based on the observations described above and the promising preclinical data, adoptive Treg therapy in transplant patients is a new therapeutic option to minimize conventional immunosuppression. Recent studies have reported the safety, efficacy, and feasibility of Treg therapy in transplant recipients (8–10). Treg therapy may contribute to the tapering of triple immunosuppression to low-dose tacrolimus monotherapy (8). However, immunosuppressive drugs may reduce the efficacy of Treg therapy. Thus, modified immunosuppressive drugs should be used to retain the efficacy of Treg therapy. Using a graft-*versus*-host disease model, Landwehr-Kenzel et al. showed that the administration of cyclosporine A–but not corticosteroids–along with Tregs had significant positive effects. In conclusion, the early control of inflammation and inhibition of genes involved in DC maturation (*i.e.*, *IRAKs*) or adoptive Treg therapy (ideally with gene-edited immunosuppressive drug-resistant Tregs) can support posttransplant immunoregulation, allowing to minimize long-term immunosuppression.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T Cells and Human Disease. *Annu Rev Immunol* (2020) 38:541–66. doi: 10.1146/annurev-immunol-042718-041717

2. Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, et al. Functional Delineation and Differentiation Dynamics of Human CD4+ T Cells Expressing the FoxP3 Transcription Factor. *Immunity* (2009) 30(6):899–911. doi: 10.1016/j.immuni.2009.03.019

3. Braza F, Dugast E, Panov I, Paul C, Vogt K, Pallier A, et al. Central Role of CD45RA– Foxp3hi Memory Regulatory T Cells in Clinical Kidney Transplantation Tolerance. *J Am Soc Nephrol* (2015) 26(8):1795–805. doi: 10.1681/ASN.2014050480

4. Mirzakhani M, Shahbazi M, Akbari R, Oliaei F, Asgharpour M, Nikoueinejad H, et al. Reduced CD4+ CD25++ CD45RA– Foxp3hi Activated Regulatory T Cells and its Association With Acute Rejection in Patients With Kidney Transplantation. *Transplant Immunol* (2020) 60:101290. doi: 10.1016/j.trim.2020.101290

5. Schaier M, Seissler N, Schmitt E, Meuer S, Hug F, Zeier M, et al. DRhigh+ CD45RA—Tregs Potentially Affect the Suppressive Activity of the Total Treg Pool in Renal Transplant Patients. *PloS One* (2012) 7(3):e34208. doi: 10.1371/journal.pone.0034208

6. Mirzakhani M, Shahbazi M, Shamdani S, Naserian S, Mohammadnia-Afrouzi M. Innate Immunity: Trained Immunity and Innate Allorecognition Against the Allograft. *Int Rev Immunol* (2021) 41(2):275–82. doi: 10.1080/08830185.2021.1921175

7. Roemhild A, Otto NM, Moll G, Abou-El-Enein M, Kaiser D, Bold G, et al. Regulatory T Cells for Minimising Immune Suppression in Kidney Transplantation: Phase I/IIa Clinical Trial. *BMJ* (2020) 371:m3734. doi: 10.1136/bmj.m3734

8. Sánchez-Fueyo A, Whitehouse G, Grageda N, Cramp ME, Lim TY, Romano M, et al. Applicability, Safety, and Biological Activity of Regulatory T Cell Therapy in Liver Transplantation. *Am J Transplant* (2020) 20(4):1125–36. doi: 10.1111/ajt.15700

9. Harden PN, Game DS, Sawitzki B, van der Net JB, Hester J, Bushell A, et al. Feasibility, Long-Term Safety, and Immune Monitoring of Regulatory T Cell Therapy in Living Donor Kidney Transplant Recipients. *Am J Transplant* (2021) 21(4):1603–11. doi: 10.1111/ajt.16395

10. Sawitzki B, Harden PN, Reinke P, Moreau A, Hutchinson JA, Game DS, et al. Regulatory Cell Therapy in Kidney Transplantation (The ONE Study): A Harmonised Design and Analysis of Seven non-Randomised, Single-Arm, Phase 1/2A Trials. *Lancet* (2020) 395(10237):1627–39. doi: 10.1016/S0140-6736(20)30167-7