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INVITED COMMENTARY

Revisiting the link between PGD and BOS in lung transplantation: highlighting the role of tregs

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Regulatory T cells (Tregs) were originally identified as immune cells critical for the maintenance of self-tolerance and prevention of autoimmune disease. However, since their discovery in 1995, Tregs have been found to have an expanded role as master regulatory cells with simultaneous multi-directional functions in immune tolerance involving both innate and adaptive immunity [1]. Similarly, approaches to predict outcomes after lung transplantation through the translation of emerging knowledge of complex immune network continue to evolve.

Ius and colleagues from Hannover Medical School, a high-volume transplant center in Germany, completed an extensive study of 724 patients with peripheral blood evaluation of Tregs pre- and post-transplant, the largest number of patients in whom Tregs have been examined to date. They demonstrated that a subpopulation of Tregs ($CD4^{+}CD25^{high}CD127^{low}$) in the blood early after lung transplantation were responsible for a protective effect against chronic lung allograft dysfunction (CLAD), mortality, and the need for re-transplantation [2]. This study reinforced the findings of their prior *in vitro* and *in vivo* studies, which showed a pivotal role for Tregs in the regulation of immune cells that had a large impact on long-term outcomes after lung transplantation [3–5].

Notably, another recent genomic and plasma biomarker study demonstrated that innate immune activation and dysregulation play a central role in the pathogenesis of primary graft dysfunction (PGD) after lung transplantation [6]. While it has been commonly accepted that patients with PGD will likely go on to develop bronchiolitis obliterans syndrome (BOS) and CLAD, a large clinical experience published in 2018 of lung transplantation in 1500 patients over a 30-year period from Barnes Jewish Hospital in St. Louis, USA [7] showed that patients in the post lung allocation score (LAS) era had a higher incidence of severe PGD as compared with those in the pre-LAS era but still had improved long-term survival and freedom from BOS. This suggests that our current understanding of drivers of both short-term and long-term survival after lung transplantation is

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incomplete. It is essential to pursue an understanding of the shared mechanisms of PGD and BOS attributed to dysregulated T-cell function, the underlying cross talk between the adaptive immune system and the innate immune system, and how Tregs play a pivotal role.

Many questions that remain unanswered after this study should be clarified in the near future as knowledge of Treg biology continues to increase [8], demonstrating not only regulation of pathogenic CD4 + T cells, CD8 + cells, and B cells in the adaptive immune system but also important cross talk between Tregs and the innate immune system. Antibody-mediated rejection (AMR) has become an increasingly recognized contributor to acute and chronic lung allograft rejection following lung transplantation. A 2019 translational study demonstrated that Foxp3 + T cells, a subset of the Tregs residing within lung allografts, regulate AMR [9] and may play an essential role in the prevention and resolution of acute lung injuries that can lead to BOS/CLAD. In the respiratory tract, bronchus-associated lymphoid tissue (BALT), which is comprised of lymphoid aggregates with a specialized epithelium, contributes to immune regulation in lung allografts that differs notably between the lungs and other solid organs [10]. Allograft tolerance is associated with induction of BALT that is rich in Foxp3 + T cells within the graft. A central role for Tregs is quite evident in the lungs, an active immunological organ, and evolving findings should be revisited and duly translated into clinical correlations in a "bench-to-bedside" scientific manner.

While it is important to keep abreast of advancements in understanding the immunology of lung transplantation and translate such progress into clinical practice, it is also intriguing to consider approaches that utilize precision-medicine analysis in conjunction with clinical variables that have been identified as risk factors impacting long-term transplant outcomes to more accurately predict CLAD. Artificial intelligence (AI), in particular machine-learning algorithms, is one evolving technology that could be used. AI and machine-learning algorithms allow computers to identify, quantify, and interpret relationships among numerous variables to predict outcomes [11]. The outcomes after lung transplantation depend on complex interactions between donor, recipient, and surgical factors. While the establishment of a validated predictive model of survival would increase successful outcomes after lung transplantation, the conventional methods reported previously have had limitations [12]. Adding precision-medicine data may fill the gaps between key clinical variables and allow more accurate analyses for prediction through the utilization of AI technologies.

Ius and colleagues should be congratulated for their thorough and important study utilizing a large institutional database. Their results highlight future directions for clinical and translational studies to answer important questions toward the goal of overcoming the challenge of suboptimal long-term survival after lung transplantation.

Conflicts of interest

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REFERENCES

1. Kitagawa Y, Sakaguchi S. Molecular control of regulatory T development and function. *Curr Opin Immunol.* 2017; **49**: 64.
2. Ius F, Salman J, Knoefel A-K, *et al.* Increased frequency of CD4+CD25highCD127low T cells early after lung transplant is associated with improved graft survival – a retrospective study. *Transplant Int* 2020; **33**: 503.
3. Siemeni T, Knofel AK, Ius F, *et al.* Transplant arteriosclerosis in humanized mice reflects chronic lung allograft dysfunction and is controlled by regulatory T cells. *J Thorac Cardiovasc Surg* 2019; **157**: 2528.
4. Siemeni T, Knofel AK, Madrahimov N, *et al.* In vivo development of transplant arteriosclerosis in humanized mice reflects alloantigen recognition and peripheral treg phenotype of lung transplant recipients. *Am J Transplant.* 2016; **16**: 3150.
5. Salman J, Ius F, Knoefel AK, *et al.* Association of higher CD4(+) CD25 (high) CD127(low), FoxP3(+), and IL-2(+) T cell frequencies early after lung transplantation with less chronic lung allograft dysfunction at two years. *Am J Transplant.* 2017; **17**: 1637.
6. Diamond LM, Cantu E, Porteous MK, *et al.* peripheral blood gene expression changes associated with primary graft dysfunction after lung transplantation. *Am J Transplant* 2017; **17**: 1770.
7. Balsara KR, Krupnick AS, Bell JM, *et al.* A single-center experience of 1500 lung transplant recipients. *J Thorac Cardiovasc Surg.* 2018; **156**: 894.
8. Wing JB, Tay C, Sakaguchi S. Control of regulatory T cells by co-signal molecules. *Adv Exp Med Biol.* 2019; **1189**: 179.

9. Li W, Gauthier JM, Higashikubo R, *et al*. Bronchus-associated lymphoid tissue-resident Foxp3+ T Lymphocytes prevent antibody-mediated lung rejection. *J Clin Invest*. 2019; **129**: 556.
10. Shenoy KV, Solomides C, Cordova F, *et al*. Low CD4/CD8 ratio in bronchus-associated lymphoid tissue is associated with lung allograft rejection. *J Transplant* 2012; **2012**: 928081.
11. Mark E, Goldsman D, Gurbaxami B, *et al*. Using machine learning and an ensemble of methods to predict kidney transplant survival. *PLoS ONE* 2019; **14**: e0209068.
12. Grimm JC, Valero V 3rd, Magruder JT, *et al*. A novel risk score that incorporates recipient and donor variables to predict 1-year mortality in the current era of lung transplantation. *J Heart Lung Transplant*. 2015; **34**: 1449.