Transplant International

INVITED COMMENTARY

# The fate of donor cells in intestinal transplantation: friend or foe?

Friederike Martin[1] & Stefan G. Tullius[2]

1 Department of General, Visceral and Transplant Surgery, Charité, Berlin, Germany
2 Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

**Correspondence**
Stefan G. Tullius MD, PhD, Division of Transplant Surgery, Brigham and Women's Hospital, 75 Francis ST, Boston, MA 02115, USA.
Tel.: +1-617-732-6446;
fax: +1-617-582-6167;
e-mail: stullius@bwh.harvard.edu

*Transplant International* 2020; 33: 1010–1012

Received: 14 April 2020; Accepted: 15 April 2020

Intestinal transplantation (ITx) has become an established therapy for a selected group of patients with irreversible intestinal failure. Unique for ITx are surgical and immunological challenges. Outcomes have improved over time with patient survival and graft survival of 77% and 71% respectively by 1 year and 47% and 41% by 10 years, yet remaining below those of other solid organ transplants. Indeed, ITx is linked to high numbers of perioperative complications, rejections, infectious infections, and cardiovascular complications [1]. A particular challenge in addressing the complex interplay of immune responses following ITx has been the lack of longitudinal clinical studies.

The critical and broad role of innate lymphoid cells (ILCs) has received a considerable amount of attention during the last decade. ILCs that are also called lineage-negative cells (Lin-) do not express antigen-specific receptors characteristic of T or B cells (lineage-positive cells, Lin+). A subgroup of innate lymphoid cells includes noncytotoxic type 1, 2, and 3 ILCs, also termed helper innate lymphoid cells (hILCs) that are conceptualized as "innate counterpart of $T_h$ cells." hILCs play a major role in tissue homeostasis, in regeneration, and in the maintenance of mucosal barriers [2,3]. ILCs reside predominantly in mucosa-associated tissue (e.g., gut and lung). ILCs, especially subtypes ILC1 and ILC3, have recently been shown to play an important role in the development of inflammatory bowel diseases [4,5].

Of relevance, the role of ILCs and the impact of long-term persistence of this cell population on outcomes after intestinal transplants remain unclear.

Gómez-Massa and coworkers from the University Hospital 12 de Octubre, Madrid, Spain, analyzed changes in lymphocyte distribution and donor cell replacement in intestinal epithelium, in lamina propria, and in the peripheral blood of ITx recipients [6]. Patient samples were analyzed for up to 13 years after ITx, providing an unprecedented long-term assessment of lymphatic cell chimerism.

The authors were able to show that Lin- hILCs (ILC1, ILC2, and ILC3), Lin- NK cells, and Lin + cells of donor origin remained present in the epithelium and in the lamina propria of intestinal transplants over more than 10 years. The replacement of donor Lin-




doi:10.1111/tri.13623

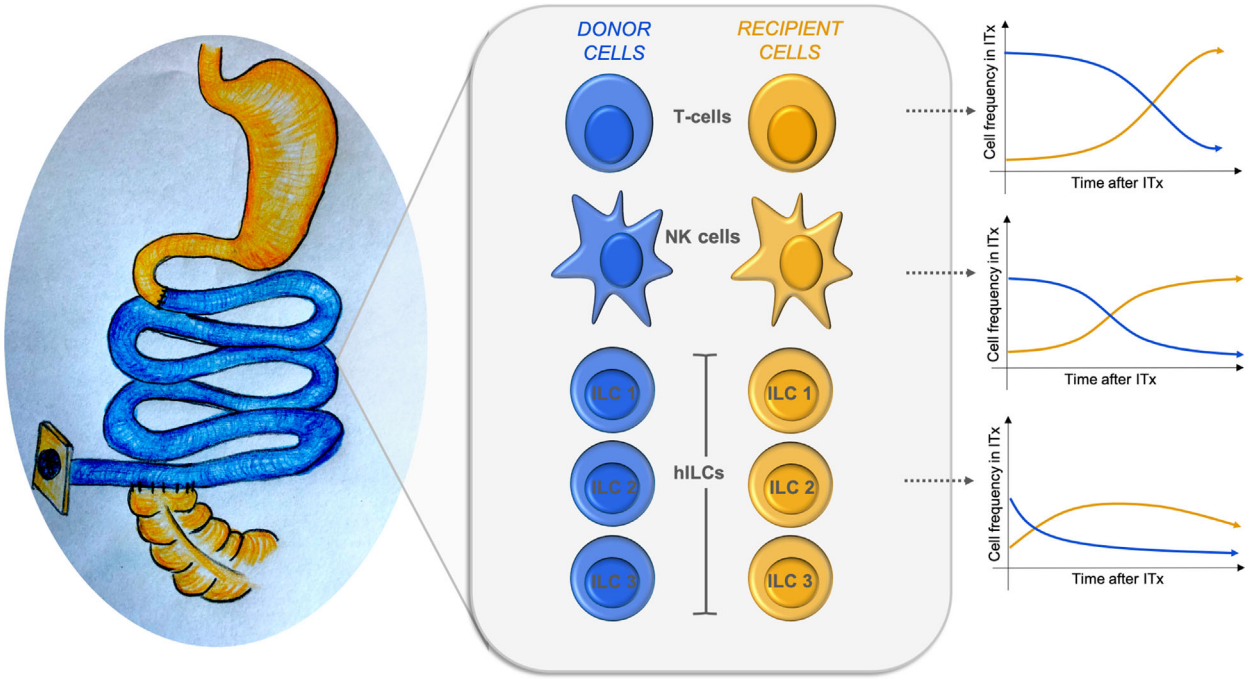


**Figure 1** Schematic illustration of donor and recipient lymphocyte distribution and replacement after intestinal transplantation. Blue cells and lines represent donor cells, and yellow cells and lines, recipient cells. The diagrams on the right represent distribution trends. ILCs, innate lymphoid cells; hILCs, helper innate lymphoid cells; NK cells, natural killer cells; ITx, intestinal transplantation.

cells with recipient Lin- cells occurred significantly earlier after transplantation than that of Lin + cells. Consistent with those observations, the chimerism of Lin + cells was more frequent than that of Lin- cells in the long term after ITx (Fig. 1). When compared to native nontransplanted intestine samples, intestinal transplant samples showed higher frequencies of hILCs and reduced amounts of Lin + cells until 10 years after transplant. Beyond 10 years, the ILC1/ILC3 ratio remained different in ITx recipients compared to those with nontransplanted intestines with an increase in ILC1 and a decrease in ILC3.

As intestinal transplants suffer from a low volume worldwide, a small series of 9 patients with a follow-up of 13 years delineating kinetics of donor and recipient immune cells presents a unique set of information [1,7]. Investigating the long-term chimerism and the distribution of Lin + and Lin- lymphatic cells in the intestinal mucosa has received thus far only a little attention and addresses relevant aspects of immunity in ITx. Although requiring confirmation in larger studies and a better insight into mechanisms, one may envision to use the ratio of Lin+/Lin- immune cells as a potential clinical biomarker. Moreover, information on clinical ratios of specific immune cells and their origin may get us closer to understand the complex immunology of intestinal transplants and to determine potential avenues leading to graft accommodation.

One concern of the study design is a selection bias, as "only" patients with long-term survival have been assessed and events during rejections or infections have not been detailed. As maintenance immunosuppression has not been uniform in this clinical study, it will be interesting to learn how differing immunosuppressive protocols may interfere with the distribution of specific donor and recipient immune cells. Moreover, with worldwide low volumes of intestinal transplants, it may be helpful to bring the reported findings back to relevant preclinical models to delineate underlying mechanisms.

Taken together, Gómez-Massa and coworkers demonstrated that donor hILCs can be found in intestinal grafts in the long term after ITx. The presence of this donor cell population appears to be beneficial, potentially contributing to graft accommodation. The unique long-term kinetic analysis of immune cells may serve as an impetus for more clinical and preclinical studies that will improve our understanding of the complex immunology and outcomes after ITx.

## Funding

The authors have declared no funding.

## Conflicts of interest

The authors have declared no conflicts of interest.

## REFERENCES

1. Grant D, Abu-Elmagd K, Mazariegos G, *et al*. Intestinal transplant registry report: global activity and trends. *Am J Transplant* 2015; **15**: 210.
2. Vivier Eric, Artis David, Colonna Marco, *et al*. Innate lymphoid cells: 10 years on. *Cell* 2018; **174**: 1054.
3. Hazenberg MD, Spits H. Human innate lymphoid cells. *Blood* 2014; **124**: 700.
4. Li J, Glover SC. Innate lymphoid cells in inflammatory bowel disease. *Archivum Immunologiae et Therapiae Experimentalis* 2018; **66**: 415.
5. Zeng B, Shi S, Ashworth G, Dong C, Liu J, Xing F. ILC3 function as a double-edged sword in inflammatory bowel diseases. *Cell Death Dis* 2019; **10**: 315.
6. Gómez-Massa E, Lasa-Lázaro M, Gil-Etayo FJ, *et al*. Donor helper innate lymphoid cells are replaced earlier than lineage positive cells and persist long-term in human intestinal grafts - a descriptive study. *Transpl Int* 2020; **33**: 1016.
7. Weiner J, Zuber J, Shonts B, *et al*. Long-term persistence of innate lymphoid cells in the gut after intestinal transplantation. *Transplantation* 2017; **101**: 2449.