CORRESPONDENCE

Letter to the Editor on "CD4+ T cells persist for years in the human small intestine and display a TH1 cytokine profile"

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We read and appreciated the recent study by Bartolome'-Casado R et al.[1]: the authors examined the turnover of CD4+ T cells in human transplanted duodenum, showing that the majority of CD4+ T cells were still donor-derived 1 year after transplantation and suggesting that immune-surveillance in non-lymphoid tissues is dominated by CD4+ T cell-resident populations. In their opinion most CD4+ T cells in human small intestine under normal conditions are non-circulating, resident cells that most likely perpetuate for years and tissue residency represents a major mechanism for CD4+ memory T cell immune-surveillance in human small bowel.

In their study transplanted patients with episodes of acute cellular rejection (ACR) or with donor-specific antibodies (DSA) were excluded. Notwithstanding, there was a large variation in persisting donor-derived CD4+ T cells among human duodenal grafts after 1 year: the Authors explained the phenomenon with the probability of undiagnosed intermittent rejection episodes (or other clinical problems) among patients between 6 and 52 weeks after transplantation. Rejection episodes dramatically increase the replacement kinetics of immune cells and microchimerism[2].

Furthermore, the Authors showed that intestinal CD4+ resident memory T cells were very potent cytokine producers through their cytotoxic granules: a fraction of them produced granzyme-B (>40%) and perforin after activation. In our previous study[3], we showed that granzyme-B and perforin are reliable blood markers of ACR after intestinal transplantation, whose activation in cytotoxic T lymphocytes and natural killer cells induces apoptosis of target cells. In the early phases after intestinal transplantation (3–28 days) the blood levels of granzyme-B and perforin increase physiologically making the interpretation of the tests difficult in case of early ACR, while later granzyme-B and perforin showed the ability to predict the onset of ACR in advance, irrespectively of the clinical symptoms or endoscopic biopsy findings.

In our study, a spike of expression of both markers was clearly detectable several days before the clinical/endoscopic/histological onset of ACR. This gap between the early blood test positivity of granzyme-B and perforin and the later onset of the ACR symptoms was explained by us with the latency time required by the recipient activated circulating lymphocytes (expressing granzyme-B and perforin) to migrate into the graft in order to cause tissue injury.

We would like to have the opinion of the authors on the following issue, based on their more recent findings: the large amount of granzyme-B or perforin, showed by our study in the blood of transplanted patients several days before the clinical symptoms of ACR, has been produced by activated recipient "circulating" lymphocytes (as speculated by us) or it could have been produced by activated donor-derived "resident" lymphocytes following the theory that immune-surveillance is always dominated by resident populations?

The matter does not represent a futile topic under the immunosuppressive point of view. Nowadays immunosuppression for intestinal transplantation is mainly based on preconditioning protocols[4] where a recipient pretreatment is administered prior to revascularization with an i.v. infusion of thymoglobulin or alemtuzumab, but at the end of the 90, experimentally and later clinically[4,5], elimination by ex vivo irradiation of mature resident lymphoid elements from the bowel allografts was known to eliminate the GVHD risk, followed by infusion of donor bone marrow cells in recipients to improve tolerogenesis. Unfortunately at that time granzyme-B and perforin were still not tested in intestinal graft recipients.

We thank you in advance the authors for their kind reply and congratulate them for their effort in such a demanding field.

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REFERENCES

1. Bartolomé-Casado, R. et al. CD4+ T cells persist for years in the human small intestine and display a TH1 cytokine profile. *Mucosal Immunol.* **14**, 402–410 (2021).
2. Weiner, J. et al. Long-term persistence of innate lymphoid cells in the gut after intestinal transplantation. *Transplantation* **101**, 2449–2454 (2017).
3. Altimari, A. et al. Blood monitoring of granzyme B and perforin expression after intestinal transplantation: considerations on clinical relevance. *Transplantation* **85**, 1778–1783 (2008).
4. Abu-Elmagd, K. M. et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. *Ann. Surg.* **250**, 567–581 (2009).
5. Murase, N. et al. Immunomodulation for intestinal transplantation by allograft irradiation, adjunct donor bone marrow infusion, or both. *Transplantation* **70**, 1632–1641 (2000).

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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