CORRESPONDENCE

Response to Lauro and Zorzetti

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We thank Lauro and Zorzetti for their interest in our work. They raise the important question whether passenger donor T cells following the intestinal graft enter the circulation after transplantation and contribute to the population of activated cytotoxic T cells found in peripheral blood.[1] We have studied the turnover and function of both CD4 and CD8 T cells in pancreaticoduodenal transplants.[2,3] In this procedure, only a small piece of duodenum devoid of gut-associated lymphoid tissue (GALT) and lymph nodes is transplanted.[4] We find that the majority of intestinal T cells are long-lived and both CD4 and CD8 Trm cells produce significant amounts of granzyme-B and perforin after activity.[2,3] Notably, non Trm (CD103-) CD8 T cells present higher constitutive expression of granzyme and perforin (without stimulation), in line with other recent reports.[5] However, in our clinical setting we do not believe that donor gut Trm cells contribute to the population circulating T cells. Firstly, the piece of transplanted duodenum is very small, and secondly, flow cytometry analysis of peripheral blood did not provide evidence of any donor cells post-transplantation. However, our transplantation setting is very different from that in the paper by Altimari et al.[1] In the latter report, they studied patients receiving large intestinal and multivisceral transplants, in which many patients show macrochimerism (more than 4% donor T cells) in peripheral blood.[6] Moreover, it was recently shown by Fu et al. that donor T cells from intestinal allografts can enter the patient's bone marrow, become activated and kill host T cells.[7] Based on this recent report, it is plausible that donor T cells may contribute to the population of cytotoxic T cells found in peripheral blood by Altimari et al.[1]

Currently, the success of intestinal transplantation is limited by high rejection rates and the risk of GVHD.[8,9] Interestingly to this end, in our pancreatoduodenal transplants we found that only 6 out of 113 patients showed histological signs of acute cellular rejection (ACR) in the duodenal segment.[10] How can this apparent difference in rejection rates be explained? In our clinical setting, dendritic cells and macrophages were replaced within weeks or month,[11,12] whereas 40–50% of the T cells were replaced 1 year after transplantation.[2,3] This tissue chimerism could cause both host versus graft (HvG) and graft versus host (GvH)-related rejection.[13] However, the low number of ACR cases suggest that HvG or GvH reactions might not occur, or alternatively that GvH T cells kill off incoming HvG T cells. In stark contrast to our transplantation setting, intestinal and multivisceral transplants involve GALT (e.g., Peyers patches) and mesenteric lymph nodes. Recipient naïve and central memory T cells may enter these lymphoid structures and become activated by donor APCs. It is reasonable to suggest that this alloresponse leads to an expansion of activated HvG T cells that enter the circulation, as proposed by Lauro and Zorzetti.

Together, these data suggest that HvG T cells activated in donor APCs in transplanted lymphoid tissue play a key role in ACR. Thus, elimination of host APCs residing in grafted lymphoid tissues may have therapeutic value. As pointed out by Lauro and Zorzetti, irradiation of mature resident lymphoid elements in the intestinal graft has been shown to reduce the risk of GVHD. However, this is a double-edged sword as durable mixed chimerism has protective effects against allograft rejection.[7]

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AUTHOR CONTRIBUTIONS

R.B.C., E.B. and F.L. wrote original draft and provided final approval.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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