The Generation of Donor-Specific CD4\(^{+}\)CD25\(^{+}\)CD45RA\(^{-}\) Naive Regulatory T Cells in Operationally Tolerant Patients After Pediatric Living-Donor Liver Transplantation

Hanaa Nafady-Hego, Ying Li, Hidenori Ohe, Xiangdong Zhao, Naoki Satoda, Shimon Sakaguchi, Kathryn Wood, Shinji Uemoto, and Takaaki Koshiba

Abstract:

Background. CD4\(^{+}\)CD25\(^{+}\)CD45RA\(^{-}\) cells (naïve regulatory T cells [naïve-Tregs]) have been identified as a functionally premature form of CD4\(^{+}\)CD25\(^{+}\)CD45RA\(^{-}\) cells (conventional-Tregs). However, their contribution to transplant tolerance remains to be elucidated. Method. We examined the frequency and the function of conventional and naïve-Tregs in the peripheral blood derived from operationally tolerant patients after pediatric living-donor liver transplant (Gr-tol). The data were compared with those of patients who were unable to be weaned off immunosuppression due to rejection (group-intolerance [Gr-intol]), patients in the process of weaning immunosuppression (Gr-weaning) and healthy volunteers (group-healthy volunteers [Gr-vol]). Results. In Gr-tol, the frequency of conventional-Tregs was significantly higher than that in Gr-vol and tended to be higher than that in Gr-intol. The frequency of naïve-Tregs was significantly decreased in Gr-intol versus those in Gr-tol, -weaning, and -vol. In mixed lymphocyte reactions, donor-specific hyporesponsiveness of CD4\(^{+}\) cells was observed only in Gr-tol but not in the other groups. Depletion of conventional or naïve-Tregs from CD4\(^{+}\) cells demonstrated that the suppressive properties of donor antigen-reactive conventional and naïve-Tregs were upregulated compared with those of third-party antigen-reactive conventional and naïve-Tregs in Gr-tol only. Conclusions. This is the first report providing detailed evidence that donor-specific naïve-Tregs were generated and their suppressive properties were upregulated in the peripheral blood of tolerant patients, whereas their frequency was downregulated in intolerant patients. Therefore, we speculate that not only conventional-Tregs play a role in Tx tolerance but also the role of naïve-Tregs is critical.

Keywords:

Humans, Living-donor liver transplantation, Tolerance, Regulatory T cells.

Published In:

Transplantation, December 27, Vol. 90, No. 12,