TOLERANCE

The origins of colonic T_{Reg} cells

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It has been previously suggested that thymus-derived regulatory T (T_{Reg}) cells primarily recognize self antigens, whereas peripherally derived T_{Reg} cells respond to foreign antigens. Indeed, conversion of forkhead box P3 (FOXP3)⁺CD4⁺ T cells to FOXP3⁺ T_{Reg} cells is known to be favoured by the tolerogenic microenvironment of the gut, where there is an abundance of innocuous foreign antigens, including food- and microbiota-derived components. However, Cebula *et al.* now suggest that most colonic T_{Reg} cells, including T_{Reg} cells that recognize intestinal commensal bacteria, develop in the thymus.

The authors used transgenic mice that express a limited but diverse T cell receptor (TCR) repertoire (TCR^{mini} mice) to investigate the origin of colonic T_{Reg} cells on the basis of high-throughput TCR sequencing analyses. T cells from TCR^{mini} mice express a single TCR

β-chain combined with a variety of TCR α-chains, and their development and function was found to be comparable to that of non-transgenic T cells.

Sorted individual FOXP3⁺ T cells and FOXP3⁺CD4⁺ T cells from the thymus, peripheral lymph nodes and intestines of TCR^{mini} mice were analysed in terms of the complementarity determining region 3 (CDR3) sequence of the TCR α-chain that they expressed. It was found that the most abundant TCRs did not overlap between the FOXP3⁺ and FOXP3⁺CD4⁺ T cell subsets, irrespective of the organ of origin. Moreover, 86% of the TCRs from colonic T_{Reg} cells were identical to 50% of the TCRs from FOXP3⁺CD4⁺ thymocytes. This suggests that in all organs that were analysed, including the intestines, peripheral conversion of FOXP3⁺CD4⁺ T cells to FOXP3⁺ T_{Reg} cells did not account for the

majority of T_{Reg} cells. A similar result was observed in transgenic mice that had an even broader TCR repertoire. So, colonic T_{Reg} cells seem to derive predominantly from FOXP3⁺CD4⁺ thymocytes.

But do these thymus-derived intestinal T_{Reg} cells respond to foreign antigens such as those derived from commensal bacteria? Treatment of TCR^{mini} mice with antibiotics altered the frequency of the most dominant colonic T_{Reg} cell TCRs, which probably reflects the antigen-specific expansion or contraction of colonic T_{Reg} cell populations. However, the diversity of the colonic T_{Reg} cell TCR repertoire was not reduced following the changes in the composition of colonic microbiota. Moreover, most colonic T_{Reg} cell TCRs were shared with FOXP3⁺CD4⁺ thymocytes even after treatment with antibiotics. This indicates that changes in the composition of the population of intestinal commensal bacteria did not promote substantial recruitment of peripherally derived T_{Reg} cells.

Finally, hybridomas that were generated from colonic T_{Reg} cells showed responsiveness to sterile filtrates of caecal contents and to sonicates of individual commensal bacterial species. As 90% of the TCRs of hybridomas that responded to caecal contents were expressed by FOXP3⁺CD4⁺ thymocytes, the authors conclude that thymus-derived T_{Reg} cells have a leading role in establishing intestinal T cell tolerance against microbiota.

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