REGULATORY T CELLS

Taking the right route

The appropriate localization of regulatory T (T_{Reg}) cells is important to ensure that they suppress any unwanted or over-exuberant immune response. But how important is T_{Reg} cell migration to the draining lymph nodes (DLNs) versus the inflamed tissue or transplanted graft for their function? Bromberg and colleagues now show that T_{Reg} cells sequentially migrate from inflamed tissues to the DLN in an islet allograft model and that this migration pattern is necessary for the optimal suppressive function of T_{Reg} cells and islet graft survival.

To examine the migration of T_{Reg} cells to a site of inflammation and/or DLNs, the authors intravenously transferred T_{Reg} cells into mice with an islet allograft (which was inflamed owing to the alloreactive T cell response) and found that T_{Reg} cells migrated to both the islet graft and the DLN, as expected. The authors then intravenously transferred T_{Reg} cells that did not express specific CC-chemokine receptors (CCRs) or selectins that are known to have a role in T_{Reg} cell migration. They found that migration from the blood to the islet graft required the expression of E-selectin and P-selectin, CCR2, CCR4 and CCR5. By contrast, migration to the DLN required the expression of CCR7 and L-selectin. Of interest, T_{Reg} cells that could migrate to the islet graft but not the DLN prolonged graft survival, whereas T_{Reg} cells that could migrate to the DLN but not the islet graft did not prolong graft survival. This indicates that T_{Reg} cell migration to the islet graft is required for its survival.

The local transfer of T_{Reg} cells to the same site as the islet graft resulted in higher numbers of T_{Reg} cells in the DLN compared with intravenous transfer, suggesting that T_{Reg} cells migrate from the graft to the DLN. This process was shown to require the expression of CCR2, CCR5 and CCR7. In addition, the local transfer of T_{Reg} cells further prolonged graft survival compared with intravenously transferred T_{Reg} cells. However, T_{Reg} cells that could not migrate to the DLN after local transfer did not further prolong graft survival, indicating that T_{Reg} cell migration from the islet graft to the DLN, in addition to migration to the islet graft, is necessary for optimal T_{Reg} cell function.

By comparing graft survival following local transfer of wild-type or *Ccr7*$^{-/-}$ T_{Reg} cells (which are excluded from the DLN) and intravenous transfer of wild-type or *Ccr2*$^{-/-}$ T_{Reg} cells (which are excluded from the islet graft), the authors showed that optimal graft survival required the sequential migration of T_{Reg} cells from the islet graft to the DLN. This sequential migration was necessary for the activation and differentiation of T_{Reg} cells that produced interleukin-10 (IL-10), transforming growth factor-β (TGFβ) and granzyme B.

Finally, the authors showed that T_{Reg} cells in the islet graft inhibited the migration of dendritic cells from the islet graft to the DLN in an IL-10- and TGFβ-dependent manner. T_{Reg} cells also inhibited the migration, accumulation and proliferation of effector T cells at both sites in an IL-10-dependent manner, but optimal suppression required the sequential migration of the T_{Reg} cells.

So, this study shows that the migration of T_{Reg} cells to islet grafts is required for allograft survival but that the sequential migration of T_{Reg} cells from the islet graft to the DLN is required for optimal T_{Reg} cell suppression and inhibition of effector T cell responses.

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