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MAST CELLS

Mast cells and T_{Reg} cells join forces

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A surprising role for mast cells in $CD4^+CD25^+$ regulatory T (T_{Reg})-cell-dependent tolerance is described in a paper by Noelle and colleagues published in *Nature*.

Recent studies have shown that genes that are mainly expressed by mast cells are overexpressed in tolerated allografts. Therefore, the authors examined the involvement of mast cells in the induction of tolerance to allografts. To do this, they used a skin-transplantation model that involved the intravenous infusion of allogeneic cells together with CD40-ligand-specific antibody, a treatment that allowed the long-term acceptance of allogeneic skin grafts in mice.

In this model, non-tolerant control groups rejected allografts ~2 weeks after transplantation. To analyse the infiltrating cells during tolerance or rejection, mice were given a second skin allograft 30 days after the first skin allograft, and this second graft was harvested 7 days later.

As expected, genes associated with T_{Reg} cells — which have previously been shown to have an important role in allograft tolerance — were highly upregulated in the skin allografts of the tolerant group of mice. All mast-cell-associated genes that were examined were also found to be upregulated in this group compared with the non-tolerant group. Confirming these results, immunohistochemical analysis of the cellular infiltrates in the allografts revealed the presence of $CD117^+$ (also known as KIT^+) mast cells in allografts that were tolerated. These cells were noticeably absent from allografts that were rejected. In addition, substantial infiltration of T_{Reg} cells was observed in the tolerated allografts. Therefore, the infiltration of both mast cells and T_{Reg} cells is increased in allografts that are tolerated.

The presence of mast cells in allografts, however, does not confirm that these cells have a functional role in the induction of tolerance. Therefore, the ability of mast-cell-deficient mice to accept skin allografts was assessed using the same model. It was found that long-term allograft tolerance could not be established in these mice. Interestingly, local reconstitution of mast cells at the site of the allograft extended graft survival in mast-cell-deficient mice, indicating that mast cells have a crucial role in skin-transplant tolerance.

But what is the link between mast cells and T_{Reg} cells? Analysis of activated T_{Reg} cells *in vitro* showed that these cells produce large amounts of the mast-cell growth factor interleukin-9 (IL-9). IL-9 was detected in tolerated skin allografts but not in syngeneic grafts, indicating a link between IL-9, mast cells and tolerance. To establish this link definitively *in vivo*, recombinant-activating gene (RAG)-deficient mice (which are devoid of all T and B cells but do have mast cells) were used in a reconstitution system. Following transplantation of skin allografts, purified $CD8^+$ T cells (which mediate graft rejection), with or without T_{Reg} cells, were transferred to these mice. The presence of T_{Reg} cells delayed the onset of allograft rejection, a process that could be completely reversed by treatment with IL-9-specific antibody. Treatment with this antibody was also associated with the presence of fewer mast cells in skin allografts. Because $CD8^+$ T cells do not produce IL-9, the authors concluded that IL-9 produced by T_{Reg} cells facilitates the accumulation of mast cells in allografts, resulting in the suppression of alloreactive $CD8^+$ T cells.

This study presents a new paradigm by which T_{Reg} cells might operate and identifies a novel role for mast cells in T_{Reg}-cell-dependent allograft tolerance.

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ORIGINAL RESEARCH PAPER Lu, L.-F. *et al.* Mast cells are essential intermediaries in regulatory T-cell tolerance. *Nature* **442**, 997–1002 (2006)