

# CD4<sup>+</sup>Foxp3<sup>+</sup> T CELLS IN TOLERANT CARDIAC ALLOGRAFTS

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## Background

Previous studies have demonstrated that anti-CD40L or anti-B7 require the presence of CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells (Treg) to induce antigen specific hypo-responsiveness. Other tolerance strategies involving Treg have shown a dependency on IL-10. The objective of this study was to investigate the role of natural Treg and IL-10 when treating transplant recipients with CTLA4Ig, anti-CD40L and anti-LFA-1.

## Methods

Recombinase activating gene-deficient (*Rag1*<sup>-/-</sup>) mice were transplanted with BALB/c hearts and adoptively transferred with *IL-10*<sup>-/-</sup> CD4<sup>+</sup> T cells, CD4<sup>+</sup>CD25<sup>-</sup> T cells or CD4<sup>+</sup>CD25<sup>-</sup>CD103<sup>-</sup> T cells and treated with costimulation blockade. Intra-graft T cells from C57BL/6 recipients were analysed for the expression of the Foxp3 protein after tolerance induction.

## Results

Mice reconstituted with *IL-10*<sup>-/-</sup> CD4<sup>+</sup> T cells, CD4<sup>+</sup>CD25<sup>-</sup> T cells or CD4<sup>+</sup>CD25<sup>-</sup>CD103<sup>-</sup> T cells and treated with costimulation blockade accepted allografts permanently. Analysis of cells from recipient mice adoptively transferred with CD4<sup>+</sup>CD25<sup>-</sup> T cells contained a population of CD4<sup>low</sup>CD25<sup>+</sup> T cells 100 days after transplantation. Costimulation blockade prevented the homeostatic proliferation of CD4<sup>+</sup>CD25<sup>-</sup>CD103<sup>-</sup> T cells in *Rag-1*<sup>-/-</sup> recipients. Accepted allografts contained an elevated number of CD4<sup>+</sup>Foxp3<sup>+</sup> T cells.

## Conclusions

These results indicate that T cell derived IL-10 is not essential for induction of graft acceptance in mice treated with costimulation blockade, but that treatment limits T cell expansion in the recipients. The results further indicate that CD4<sup>+</sup> T cells depleted of regulatory cells convert into CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells in the periphery of treated mice and that intra-graft CD4<sup>+</sup>Foxp3<sup>+</sup> T cells may maintain the tolerance.