Infections erode transplantation tolerance

Organ transplantation is an effective means of treating patients with organ failure, but rejection of the graft remains a major challenge. The life-long use of immunosuppressants needed to prevent rejection makes transplant recipients more susceptible to infections and cancer. As a result, there is considerable interest in finding ways of altering the immune system of the recipient to a state of immune tolerance, so that the transplanted graft is retained without the need for continued immunosuppression while immune responses to infections and tumors are preserved. In the clinic, only a small minority of kidney transplant patients who wean themselves off of immunosuppressants do not reject their transplants and are considered tolerant. Based on experimental and clinical data, it is now appreciated that infections in tolerant hosts induce a risk of graft loss. Understanding how infections precipitate the loss of tolerance is therefore key to achieving therapies that can induce a robust tolerance that persists for the life of the transplant recipient.

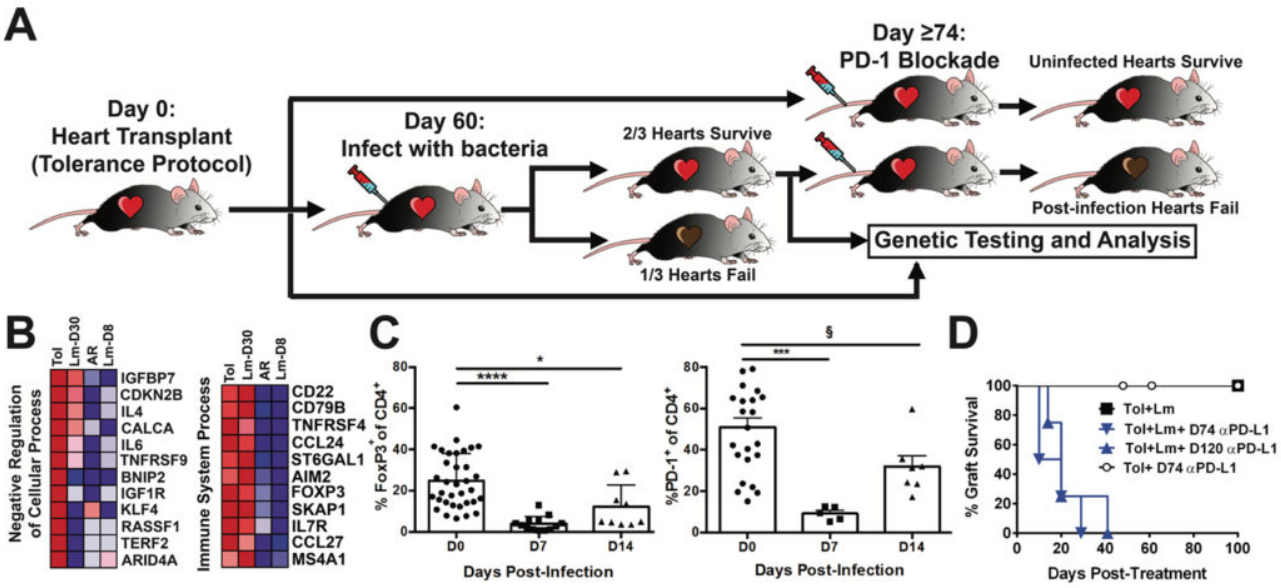

Fig. 1. A, Visual representation of experimental design. B, Sample gene expression profile comparing tolerant (Tol), Listeria infected day 8 post-infection (Lm-D8), and day 30 post-infection mice (Lm-D30). C, Summary of percentage of regulatory and PD-1 expressing cells in mice pre- and D7 & D14 post-infection. D, Comparison of heart survival in tolerant and post-infection mice subject to PD-1 blockade with anti-PD-L1.

In order to study transplantation tolerance experimentally, heart grafts were surgically implanted into genetically distinct mice transiently treated with anti-CD40L in combination with donor blood cells. This regimen induces a state of robust tolerance where the grafts continue to beat

indefinitely. Infection of these mice with the bacteria *Listeria monocytogenes* at >60 days post-transplantation, after tolerance was fully established, resulted in acute rejection of the grafts in one-third of the animals and a transient slowing down or no detectable change in heartbeat in the other two-thirds. We next tested whether the quality of tolerance had been eroded in the two-thirds post-infection, such that these recipients become more susceptible to future graft rejection.

Observations of clear differences in the genes and proteins expressed by immune cells infiltrating the grafts before and after infection supported the notion that infections had persistent effects on functionally tolerant grafts. Of particular relevance was the significant reduction, at the time of infection, of immune FoxP3^{+} regulatory T cells and of PD-1 expression. These 2 pathways inhibit immune responses and are important for the maintenance of transplantation tolerance. Importantly, the percentage of regulatory T cells and PD-1-expressing T cells were imperfectly restored after infection, and blockade of PD-1 precipitated graft rejection in post-infected but not uninfected tolerant mice, confirming that infection had eroded the quality of transplantation tolerance in post-infected mice.

Based on the readout of whether a graft is accepted or rejected after discontinuation of immunosuppression, tolerance has been viewed as an all or none phenomenon. Our studies suggest that there is a continuum of states between tolerance and rejection, and that some infections can push a stable and robust state of tolerance towards rejection, either acutely or in a stepwise manner. We propose that infections in tolerant patients need to be carefully monitored and their potential impact on the graft assessed. Our studies also suggest the need for therapies that can boost the quality of tolerance if it becomes eroded over time.

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