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Timing is everything in tolerance

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The heterotopic heart transplant model has been utilized by many investigators to assess tolerance induction strategies that have eventually wound up being tested in clinical trials of kidney transplantation. The difficulty in replicating mouse or rat tolerance strategies in humans may be due in part to a lack of understanding of the mechanisms that make a given approach successful. In the case of the combined treatment of B6 mice with BALB/c donor-specific transfusion(DST) plus anti-CD40L, previous experiments using allospecific TEa transgenic CD4 T cells had indicated that T cell anergy, occurring after a short period of T cell expansion, was the principal mode of tolerization (1).

The article by Burrell and Bromberg, “Fates of CD4+ T Cells in a Tolerant Environment Depend on Timing and Place of Antigen Exposure” in the current issue of AJT (2) brings a much greater depth to our understanding of transplantation tolerance induction by DST plus costimulation blockade. The authors used a novel fluorescent- labeling and adoptive transfer strategy, applying different fluorescent probes of cell division to examine the fate of donor-allospecific CD4 T cells during cardiac allo-transplantation at different times in the course of anti-CD40L plus DST treatment. The surprising result: anti-CD40L did not interfere with allospecific T cell proliferation induced by DST. Instead, TEa transgenic CD4 T cells proliferated and become activated—mainly in the peripheral lymph nodes—and differentiated into Treg cells, as indicated by the acquisition of Foxp3 and CD25 expression. Acquisition of Treg phenotype was not seen in mice treated with DST alone, which only induced activation (CD25) but not Foxp3. This unique effect of anti-CD40L on Treg induction had not been uncovered previously. Moreover, by the time of BALB/c heart transplantation, 7 days later, an environment had been established that inhibited naïve graft-reactive TEa cells from becoming activated and developing into either effector or regulatory lineages. Instead, the perioperatively transferred TEa cells underwent apoptosis in the absence of activation, suggesting a novel anergy → apoptosis pathway. In the absence of any tolerization, graft-reactive T cells transferred into the host proliferated—mostly in the spleen—and most underwent classical activation-induced cell death [AICD].

These new results help to reconcile previous conflicting notions of tolerance induction by DST plus co-stimulation blockade. Tolerance was not based on anergy alone, nor on Treg induction or deletion alone, but on the combination of Treg induction via immune deviation of conventional CD4 T cells, creation of a ‘tolerance environment’, and the subsequent induction of anergy and/or apoptosis of T effector cells. The authors did not dissect the basis

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of the “tolerance environment”, but based on previous work from this group and others, one hypothesis might be that the Treg cells induced by DST plus anti-CD40L alter the dendritic cell phenotypes of the host, inducing anergy rather than activation in newly arising alloreactive CD4 T cells.

One question not addressed in the study is the possible difference between direct and indirect pathway T cell responses during the evolution of allotolerance. The TEa Tg T cell, which recognizes a peptide derived from the Eαchain in the context of IA^b, is strictly an indirect pathway T cell in this fully allogeneic model (BALB/c→B6). It would be of interest to explore T cell fates using a different Tg T cell that only recognizes a direct pathway ligand.

In summary, the paper by Burrell & Bromberg provides new insights into the layers of tolerance that develop sequentially in a host challenged first with leukocytes, and later with a solid organ containing passenger leukocytes as well as parenchymal tissue. Clinicians interested in applying tolerance strategies to their patients should be alert to the potential of combining donor cells with CoS—blockade particularly with new reagents that avoid the coagulopathies associated with anti-CD40L—as well as to the difficulties posed by concomitant use of immunosuppressive drugs that may interfere with either the Treg or anergy/apoptosis phases of tolerance induction.

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