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Plasmacytoid Dendritic Cells and the Spontaneous Acceptance of Kidney Allografts

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More than forty years ago, Russell et al[1] demonstrated that 'spontaneous' acceptance of kidney allografts could occur in certain mouse MHC mis-matched strain combinations, in the absence of exogenous immune modulation. Notably, this phenomenon appeared to be both species- and organ-specific, in that kidney allografts in other species, as well as mouse heart allografts were rejected rapidly under the same conditions. In the DBA/2 to C57BL/6 mouse kidney transplant model, recipients of accepted kidney allografts were found to exhibit transforming growth factor beta (TGFβ)-mediated inhibition of donor-reactive T cell responses.[2] Subsequent studies have demonstrated that spontaneous kidney allograft acceptance is dependent on the development of donor-specific regulatory T cells (Treg).[3,4] Furthermore, spontaneous acceptance of kidney allografts has been associated with the development of Treg-rich organized lymphoid structures (TOLS) within the grafts.[4] While early acceptance of mouse kidney allografts can be Treg-dependent, their long-term survival is associated with a progressive increase of intra-graft indoleamine dioxygenase (IDO) gene expression, likely mediated by regulatory dendritic cells (DCreg).[5]

Plasmacytoid dendritic cells (pDC) are a unique population of unconventional antigen-presenting cells (APC) that regulate and integrate innate and adaptive immune responses. The function of pDC was identified initially during immune responses to viral infection and defined mainly by their production of type I interferons. Meanwhile, experimental and human studies suggested that pDC played a key role in the maintenance of mucosal tolerance,[6] where elimination of pDC (using pDC-depleting antibodies) prior to antigen (Ag) exposure resulted in the abrogation of tolerance. Adoptive transfer of poietin (fms-like tyrosine kinase 3 ligand)-mobilized bone marrow-derived pDC precursors or freshly-isolated splenic pDC was then shown to prolong mouse heart allograft survival in untreated or immunosuppressed recipients.

In this issue of *Transplantation*, Oh et al[7] have explored the role of pDC in the spontaneous acceptance of DBA/2 kidney allografts in C57BL/6 recipients, with no immunosuppression.

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Six weeks after transplantation, TOLS enriched for forkhead box p3 (Foxp3)$^{+}$ Treg and plasmacytoid DC Ag (PDCA)-1^{+} cells were observed in the grafts. By contrast, using the reverse strain combination, C57BL/6 grafts were rejected acutely (within 8 days) by DBA/2 recipients, with no TOLS formation. Compared to pDC isolated from native kidneys, pDC isolated from the accepted kidney allografts expressed high levels of the Ig superfamily member Siglec-H,- a marker specific for murine pDC. Interestingly, 6 weeks after transplantation, the majority of graft-infiltrating recipient pDC were positive for donor MHC Ag (I-A^{d}), suggesting "cross-dressing" of pDC in the accepted allografts. Such cross dressing of graft-infiltrating DC (conventional myeloid DC) that regulate anti-donor T cell reactivity, has been described recently in the context of spontaneous acceptance of mouse liver allografts.[8]

Additionally, in their study, Oh et al have demonstrated that "strain-specific" pDC-mediated induction of suppressive Treg in vitro correlates with in vivo enhanced allograft acceptance. Inhibition of MEK/ERK and nuclear factor (NF)κB signaling prevented Treg induction by the pDC. After co-culture with DBA/2 pDC in the presence of IL-2 and TGFβ, responder C57BL/6 CD4^{+}CD25^{-} T cells upregulated Foxp3 expression. Moreover, adoptive transfer of the induced C57BL/6 Treg significantly prolonged DBA/2 heterotopic heart allograft survival in C57BL/6 recipients, without immunosuppressive therapy. Meanwhile, the authors did not observe a similar finding to that reported previously in spontaneous kidney allograft acceptance, i.e., IDO-mediated T cell regulation. While this study provides new mechanistic insights into the phenomenon of spontaneous acceptance of murine kidney allografts, future studies are warranted to validate the role of pDC in vivo. Thus, it has yet to be determined whether selective in vivo depletion of pDC in this model will result in disruption of TOLS, prevention of Treg development and abrogation of spontaneous allograft acceptance.

Clinical trials using DCreg therapy to promote long-term allograft survival/tolerance induction are currently underway (www.clinicaltrials.gov). While increasing evidence identifies pDC as a potential therapeutic target for allograft tolerance,[9] it is not known whether pDC-mediated immunoregulatory mechanisms of spontaneous allograft acceptance observed in rodents would lead to stable, long-term acceptance of kidney allografts in humans. Also, while pDC possess poor immunostimulatory abilities compared to conventional DC, they are also considered powerful APC following their maturation in response to inflammatory stimuli. In a recent study,[10] renal epithelial cells infected with cytomegalovirus produced soluble factors that induced human pDC maturation, enhanced their phagocytic function, and potentiated their immunostimulatory capacity for allogeneic CD4^{+} and CD8^{+} T cells. This later observation has implications for the capacity of pDC to preserve their tolerogenic potential in the context of clinical kidney transplantation. Finally, since human and murine pDC may differ in both their phenotype and function, rigorous pre-clinical (including testing in nonhuman primates) studies are required to validate their role and potential for promotion of kidney allograft tolerance.

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