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Dendritic cell therapy in composite tissue allotransplantation

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Abstract

Dendritic cells (DCs) are bone marrow-derived, professional antigen-presenting cells, with inherent tolerogenic function. The ability of immature or maturation-resistant DCs to regulate alloantigen-specific T-cell responses and to promote tolerance induction has been well demonstrated in organ and bone marrow transplantation. Recent data suggest that DCs can also promote long-term survival of composite tissue allografts in the absence of continued immunosuppressive drug therapy.

DENDRITIC CELLS: REGULATORS OF IMMUNE REACTIVITY WITH THERAPEUTIC POTENTIAL

In recent years, there has been a shift away from the traditional perception of bone marrow-derived dendritic cells (DCs) solely as inducers of immune reactivity and transplant rejection. The contemporary view is that these uniquely well-equipped antigen-presenting cells are crucial regulators of immunity, including their ability, as immature or maturation-resistant cells, to promote transplant tolerance in experimental animal models. Advances in our understanding of the phenotypic and functional plasticity of DCs, and in our ability to manipulate their development and maturation in vitro and in vivo, have provided a basis for the promotion of their inherent tolerogenicity. The therapeutic potential of DCs has prospective applications in both transplantation and chronic inflammatory disease.

Considerable insight has been gained into the role of DCs in central and peripheral tolerance and into the molecular pathways that regulate the outcome of DC–T-cell interactions.^{1,2} Both DC-based adoptive cell therapy and in situ targeting of DCs³ have shown promise for the promotion of transplant tolerance. Much of this information has been obtained using in vitro and small-animal model systems, and many questions remain regarding the relevance of these findings to humans. Early nonhuman primate work has characterized DCs with tolerogenic phenotype and potential, which can be used to regulate alloimmune reactivity in vivo.⁴ A major challenge in this emerging area of applied DC biology is how the accumulated knowledge can be exploited successfully to improve the outcome of clinical organ or bone marrow transplantation.⁵

Proof of the principle that human autologous DCs can induce T-cell tolerance to model antigens and induce antigen-specific T-regulatory cells (Tregs) has been demonstrated in human volunteers.^{6,7} Challenges facing tolerogenic DC therapy in transplantation include the optimum type of DCs; the form of alloantigen to be delivered to host-derived DCs; the optimal timing, route, dose, and frequency of delivery of the cells; optimal use of DCs with

immunosuppressive agents⁸; their interaction with memory T cells⁹; and defining outcomes that can be adequately monitored.²

DC THERAPY OF COMPOSITE TISSUE ALLOGRAFT REJECTION: PROMOTION OF INDEFINITE GRAFT SURVIVAL WITHOUT MAINTENANCE IMMUNOSUPPRESSION

Recent studies, conducted at the University of Pittsburgh, have demonstrated the potential of myeloid DC therapy of composite tissue allograft (CTA) rejection (Table 1). Sacks et al¹⁰ investigated whether short-term immunosuppression, combined with recipient-derived immature DCs pulsed with donor alloantigen (cell-free donor splenocyte lysate), could promote rat hind-limb allograft survival. Donor alloantigen-pulsed, recipient bone marrow-derived DCs administered intravenously on days 7 and 14 posttransplantation combined with transient T cell-directed immunosuppression (anti-lymphocyte serum [ALS] plus cyclosporine [CsA]) prolonged allograft survival significantly across a full MHC barrier. Further studies showed that posttransplantation administration of donor alloantigen-pulsed, pharmacologically modified DCs (rapamycin-conditioned¹¹) to rats given perioperative ALS and 21 days of CsA significantly delayed hind-limb allograft rejection and promoted long-term (>125 days) graft survival in 50% of the CTA recipients.¹² Additional work by Horibe et al¹³ has also demonstrated the potential of DC therapy in a rat vascularized skin allograft model. Donor alloantigen-pulsed, rapamycin-conditioned host DCs (but not control DCs) induced long-term skin graft survival (median survival time > 133 days) when administered 7 and 14 days posttransplantation to graft recipients given ALS plus 21 days of CsA. Host T cells in recipients with long-surviving grafts exhibited donor-specific unresponsiveness and prolonged survival of donor but not third-party challenge skin grafts. Both flow cytometric and immunohistochemical analyses revealed that donor alloantigen-pulsed, rapamycin-conditioned host DC infusion expanded CD4⁺ Foxp3⁺ Tregs in recipient spleens, graft-associated lymph nodes, and the allograft. Taken together, these data demonstrate that pharmacologically modified, donor alloantigen-pulsed host DCs administered postoperatively can promote indefinite vascularized skin allograft survival associated with Treg expansion. These findings may have important implications for the evaluation of DC-based “negative cellular vaccines” in CTA transplantation.

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Promotion of Indefinite Organ, Pancreatic Islet, and Composite Tissue Allograft Survival by Host-Derived “Tolerogenic” DCs* in the Absence of Continued Maintenance Immunosuppression

Table 1

DC Treatment	Host Treatment	Route of DC Injection	Graft	MST (d)	Species	Reference
Donor MHC class I peptide	None	IT	Heart	>150	Rat	14
Donor MHC class I peptide	ALS (perioperative)	IV	Pancreatic islet	>200	Rat	15
Rapamycin + donor splenocyte lysate	None	IV (×3)	Heart	>100	Mouse	16
Rapamycin + donor splenocyte lysate	Rapamycin (9 d)	IV	Heart	>100	Mouse	11
Rapamycin + donor splenocyte lysate	ALS (perioperative) + cyclosporine (21 d)	IV	Hind limb	>125	Rat	12

ALS, anti-lymphocyte serum; DC, dendritic cell; IT, intrathymic; IV, intravenous; MST, median survival time.

* Bone marrow-derived.