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Costimulatory Molecule-Deficient Dendritic Cell Progenitors Induce T Cell Hyporesponsiveness In Vitro and Prolong the Survival of Vascularized Cardiac Allografts

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Dendritic cells (DC) are specialized antigen-presenting cells for the induction of cell-mediated immunity, including graft rejection.[1] Evidence also exists, however, for their tolerogenicity.[2,3] We have previously shown that GM-CSF-stimulated mouse bone marrow (BM)-derived DC progenitors that express cell surface MHC class II antigens but are deficient in expression of the costimulatory molecules B7-1 (CD80) and B7-2 (CD86) can induce alloantigen-specific T cell anergy in vitro.[4] In the present study, we tested the in vivo relevance of these findings in a vascularized cardiac allograft model.

MATERIALS AND METHODS

C57BL/10 (B10; $H2^b$), C3H ($H2^k$), or BALB/c ($H2^d$) mouse BM-derived DC progenitors, propagated in GM-CSF as described previously,[5] were injected intravenously into normal C3H ($H2^k$) recipients. Seven days later, the mice received abdominal heart transplants from normal B10 donors.[6] No immunosuppressive treatment was given. Spleen T cells from the C3H mice seven days after the injection of DC progenitors of B10 donors were used as responder/effector cells in mixed leukocyte reaction (MLR) and cytotoxic T lymphocyte (CTL) assays. Cell surface phenotype was analyzed by flow cytometry with a panel of monoclonal antibodies.

RESULTS AND DISCUSSION

As we reported previously, B10 mouse BM-derived DC progenitors ($DEC205^+$, MHC class II^+, B7-1^{dim}, B7-2^-) induced allogeneic-specific T cell hyporesponsiveness in C3H T cells in vitro.[4] In addition, however, we found that B10 heart grafts were prolonged significantly in C3H mice that were injected intravenously with 2×10^6 of these B10 DC progenitors 7 days before transplantation [median survival time (MST) 22 days vs 9.5 days in control group]. MST was also prolonged although to a lesser extent (16.5 days) in mice that received third-party (BALB/c; $H2^d$) DC progenitors cultured under the same conditions and expressing the same phenotype. However, C3H recipients injected with “mature” GM-CSF + IL-4 stimulated B10 DC ($DEC205^+$, MHC class II^{bright}, B7-1^+, B7-2^{bright}) 7 days before transplant rejected B10 heart grafts in an accelerated fashion (MST 7 days). T cells from C3H mice given B10 B7-2^- DC progenitors seven days earlier showed very low MLR responses to donor stimulators, but those from C3H mice injected with B7-2^{bright} B10 DC showed marked proliferative responses to donor stimulators. T cells from C3H mice injected with B10 B7-2^- DC progenitors generated lower CTL activity than animals given B7-2^{bright} B10 DC. Amongst the injected donor MHC class II^+ DC progenitors that migrated to recipient secondary lymphoid tissue were cells that appeared to have unregulated cell surface B7-1 and B7-2 molecule

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expression. This observation may at least in part explain the temporary or unstable nature of the hyporesponsiveness induced by donor-derived DC progenitors in non-immunosuppressed recipients.

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