ELSEVIER

Syngeneic Bone Marrow Cells Expressing a Single Donor Class I MHC Molecule Are More Effective at Inducing Tolerance Than Donor Bone Marrow Cells

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BONE MARROW cells (BMCs) may be a useful vehicle for pretransplant alloantigen delivery to induce tolerance. Administration of donor BMCs has been shown to prolong graft survival in human and animal models.[1-4] Moreover, BMCs can promote a state of macro- or microchimerism which may be important both in the induction and maintenance of tolerance.[5,6] In this study, we have investigated the ability of BMCs expressing a single donor MHC class I molecule to induce specific unresponsiveness in vivo.

MATERIALS AND METHODS

Two main protocols were investigated. Recipient CBA.Ca ($H2^k$) mice were either given BMCs alone IV at various times before a heterotopic C57BL/10 ($H2^b$) cardiac transplant (protocol A), or BMCs (day −27) in combination with a depleting anti-Cd4 monoclonal antibody YTA3.1,[7] at day −28 and −27 before transplantation on day 0 (protocol B). BMCs were either fully allogeneic from C57BL/10 donors or from transgenic CBK mice ($CBA+K^b$) which express the donor class I molecule K^b as a transgene.[8]

RESULTS

When 5×10^6 fully allogeneic, donor ($H2^b$) BMCs were used alone (protocol A), they were completely ineffective when given 14 days before or at the time of transplantation. In contrast, long-term graft survival (LTGS) was achieved in 66% and 75% of recipients when the same dose was given 27 and 42 days before transplantation. Interestingly, when the ability of CBK ($H2^k+K^b$) BMCs to induce LTGS was evaluated using protocol A, they were found to be more effective. 5×10^6 and 5×10^7 CBK BMCs given on the day of transplantation resulted in 25% and 80% LTGS respectively. Both doses of CBK BMCs were able to induce 100% LTGS when administered 14 or 27 days before transplantation. When pretreatment with BMCs was combined with anti-Cd4 (protocol B), doses as low as 5×10^5 cells were found to be effective. Again, CBK BMCs were found to be relatively more effective; LTGS was induced in 100% of recipients when 5×10^5 CBK BMCs were used compared with 83% with the same dose of C57BL/10 BMCs.

DISCUSSION

In conclusion, BMCs are suitable vehicles for alloantigen delivery. It is not necessary to expose the recipient to the full complement of donor major and minor histocompatibility antigens to induce unresponsiveness. The addition of anti-Cd4 to the pretreatment protocol reduces the number of BMCs required by 10 fold. In our model, donor BMCs given on the day of transplantation were ineffective in prolonging graft survival in otherwise unmanipulated recipients. However, a high dose recipient-type BMCs expressing a single donor class I MHC molecule given on the day of transplantation induced LTGS in 80% of recipients. This difference between donor- and recipient-type BMCs expressing a single donor class I MHC gene may have important clinical implications.

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